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A MODERN PLAN FOR A COMMUNITY CAMPAIGN AGAINST AIR POLLUTION.*

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The invitation which brought me here is regarded by the Mellon Institute of Industrial Research as fresh evidence that medical associations in this country are giving serious consideration to the problem of air pollution, presumably with a view to exercising leadership in the promotion of preventive measures. This attitude on the part of the College of Physicians is quite in line with the accepted traditions of Philadelphia, the home of internationally famous scientific societies. Mellon Institute feels honored at being asked to collaborate with you in planning for consideration of the abatement of smoke in Philadelphia. Medical societies in other cities will watch what is done here.

Air, Water and Food Purity Equally Important. Pure air is primarily a medical consideration. Logically, its maintenance is a municipal health department responsibility, just as are pure food and pure water. In the presence of city-wide contamination of his food, his water supply or the air he must breathe, the average citizen is helpless to protect himself or the members of his family. He is compelled to take what the city offers him. When aroused to danger, his instinct and his experience tell him to turn to the physician for protection and guidance. In response to a popular demand

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of this kind, the medical profession was found in the forefront of the movements which gave municipalities pure food and pure water. A parallel movement for pure air fell short of establishing thoroughgoing control. Generally the prevention of dense smoke was about all that was aimed at. Only now is the public coming freely to understand that other and unregulated products of fuel combustion are much more harmful.

In view of the inadequacy and inconclusive character of existing legislation, and also because prompt action may bring unusually desirable economic benefits, the time seems ripe for the medical profession to reassert its leadership and to make hygienically pure air an accomplished fact. A development of this kind in medical circles would be in line with the rapid growth of preventive medicine, which includes air hygiene. The initiative and guidance of physicians are necessary to the success of the cause of air hygiene.

Since 1911 Mellon Institute has been conscious of the relevancy of medicine in formulating its research, and has consistently sustained medical interests in their work to mitigate air pollution. In that year it turned to the Pittsburgh School of Medicine for study of the hygienic aspects of the smoke problem. Oskar Klotz, then professor of pathology, and his associates undertook the study. Their comprehensive printed report of the damage done to health by products of combustion is recognized as a classic; it has been a standard work of reference for two decades.

At that time we recognized that the engineer was interested because of fuel economy and the effects of the products of combustion on constructional material. We recognized that the economist was interested from the viewpoint of waste, added expense in cleaning, loss of natural daylight and such phases of the problem. But after all was said and done, the most influential fact in the effect of air pollutants, particularly products of combustion, was health. This angle controlled the formulation of the Pittsburgh ordinance, which ordinance has served as a model for similar legislation in many cities. When the Bureau of Smoke Regulation was organized it was placed in the Department of Health—a practice that was widely followed over the country.

With the passage of years, Mellon Institute has seen success achieved in reducing the dense smoke nuisance emanating from the regulated portions of its home city, and it has consistently adhered to its policy of insisting on medical and public health participation. Even now the Institute is sustaining Ralph R. Mellon and his staff at West Penn Hospital in a study which has for its aim the more accurate determination of air-borne diseases.

In the light of the character of these developments, I come before you as one fully cognizant of the high importance of the strictly medical and public health aspects of smoke abatement.

It must be recognized that, because the physician is the store-

house of needed medical information, he therefore is the sound guide in air hygiene. He knows that inhaled solid particles irritate the sensitive membranes of the nose, throat and lungs, and may prepare a predisposition to acute diseases of the respiratory tract; that smoke and dirt in the atmosphere reduce the amount of natural sunlight received; that this reduction is proportionately greater in the shorter wave lengths, particularly in the therapeutic band of ultraviolet radiation, the natural source of vitamin D; that bright, sunny days are stimulating, while gloomy, smoky days are depressing; that smoke and dust aid in the formation and prolongation of fogs, with their coincident effects; and that, in other ways as well, bodily wellbeing is affected. The rôle of the physician is fundamental; he is looked to by the public to point out health hazards and to work for their elimination; and he is equipped to set the standard for atmospheric cleanliness—a standard which the engineer will then arrange to meet. The public commitment of the physicians in a community to a campaign for pure air will have as much force as the combined arguments of all other protagonists.

Smoke Regulation. With exceptions so few as practically to be negligible, cities that have anti-smoke ordinances regulate only dense smoke. Generally speaking, this means that, unless the density is such that it is impossible to see through the column of smoke as it leaves the stack, there is no violation. And even this opaque smoke is permitted for periods ranging from 1 minute in 8 consecutive minutes to 6 or 8 minutes in 1 hour. Thus it is allowable for a stack to smoke continuously, unless the duration of *opaque* smoke exceeds the time limit. And, of course, solids that do not color the smoke stream, and noxious and obnoxious gases, are not included in the prohibition.

Ordinances prescribe that only such equipment may be installed as can be operated within the limits set, with no provision for reducing those limits as an incentive to manufacturers to produce more advanced designs. After this equipment is installed and in operation, enforcement becomes a matter of observation and supervision on the part of the city inspectors. It is obvious that, under such conditions, results will be in direct proportion to the number of inspectors and their efficiency. Cities have not felt justified in employing large enough inspectional forces for close, continuous control. Consequently, while in many communities it has been possible to maintain a fair degree of compliance, in others enforcement has been little more than a gesture.

The volume of stack dirt is proportional to the amount and smoke-making possibilities of the fuel used. The use of automatic stokers and of semi-smokeless boilers, smokeless fuels in boilers not designed for high volatile coal, better firing methods—all have aided in reducing the amount of visible smoke. The good that might be accomplished has been limited by failure to regulate light smoke

and to exercise control over cinder and ash. Then, too, in all except a few instances, private homes and the smaller apartment houses have been exempt from any regulation as to equipment, fuel or smoke. The necessity for control of domestic smoke-making has been very definitely emphasized during the past three winters. With industrial activity at a low ebb, it has been possible clearly to see the part played by the heating plants in maintaining a smoke nuisance.

The wind is depended upon to carry away the finer solids and to distribute them over wide areas. As the carrying power of the wind is proportional to its velocity, it follows that a low velocity will bring higher concentrations in limited areas, often resulting in formation of a smoke pall or aggravation of one already formed.

Smoke abatement as it has been practised has been instrumental in greatly reducing the amount of visible smoke, in effecting material individual savings in fuel cost, in providing a cleaner atmosphere than formerly with a higher percentage of sunshine, and in reducing cleaning and lighting bills. In other ways as well, smoke abatement has been of tremendous benefit. There is no argument against it; but we still have a smoke nuisance, largely because the extent to which smoke and stack dust can be eliminated has not generally been understood.

Early ordinances necessarily were compromises. A minority protest was smothered by a majority belief that smoke and prosperity were inseparably connected; plant owners feared possible unreasonable restrictions through unintelligent or unsympathetic enforcement; limitation of the amount of smoke to be permitted had to be made in the light of current combustion practice and availability of equipment designed without any such definite restriction; home owners did not take kindly to the idea of regulation, although willing and often eager to have the industrial and commercial plants controlled.

Later ordinances throughout the country generally have been patterned after those earlier compromises. As a result, the advance in smoke abatement has been neither as rapid nor as great as it could have been. The market affords better fuel-burning equipment than ever before; a large percentage of these devices could meet requirements much more strict than those now in force. It would seem wise, from the standpoint of efficiency as well as of cleanliness, to take full advantage of what has been done and to press for additional advances.

Further limiting the effectiveness of smoke abatement is the inability of a city to exercise any control beyond its geographic limits. Manufacturing centers usually are surrounded by smaller industrial communities in which there is little or no regulation of smoke. Wind-borne products of combustion from each such community are carried over and into every other in the group, so that

effort on the part of the central city to clean up is made less decisive by the effects of contaminants originating in parts of the area over which it has no jurisdiction. It is obvious that there should be either unified control or uniform regulation throughout the district.

Another reason for the failure of smoke abatement (as it has been carried on) to meet with the full measure of success that might have been expected is that it has not had the continuous active backing of the community. After an ordinance is passed and a city bureau is charged with the enforcement, most of those who were active in stimulating public opinion and securing enactment of the necessary law regard their civic duty as completed. They, therefore, fold their hands and sit back to watch an inadequately manned enforcement machine operate. Gradually, as the road to cleanliness becomes steeper and more rocky, the machine slows up or even slips backward. There is a demand for a new driver, when the fault lies not with him, nor perhaps with the machine; the road-mending force has quit work. To be permanently successful, smoke abatement like any other constructive program must have the solid support of the people. Passivity is much more difficult to combat than resistance.

Stricter Regulation. Considering the fact that equipment is available to satisfy much more stringent requirements than are now being applied with more or less success, it is comparatively easy to indicate the limits to which existing ordinances could be raised or which could be set for new ones.

1. By proper selection from among the large number of makes of boilers, furnaces, automatic feeds and control, and with intelligent care, *dense* smoke could be eliminated in normal operation. The allowance for *light* smoke would vary; in communities where only smokeless fuel is used, restriction could be greater than in sections where high volatile coal is used and where the degree of smokelessness depends upon the equipment and its operation and not on the fuel.
2. Alterations and repairs could be made to conform to such rules and regulations as would insure the same degree of smokelessness.
3. A reasonable time could be allowed for compliance by those whose plants were installed before restrictions were imposed. Serviceable units need not be scrapped, but could be regulated within reason.
4. The use of dust separators would make it possible to eliminate most of the ash nuisance from solid fuels.
5. Ordinances should allow no exemptions—there should be no preferred class. Laws should be framed in such a way that, without the necessity of formal revision by councils, advantage may be taken from time to time of the rapid advances that will be made toward smokeless and dustless use of fuels.

Campaign for Pure Air. The familiar type of smoke abatement campaign has features which must be included in any movement toward pure air. It provides for the essential stimulation of public opinion; it affords an opportunity for a considerable amount of valuable general education; it prepares the way for needed legisla-

tion. All of these are necessary, and every community has some public-spirited persons, accustomed to lead in civic matters, who will be found willing to organize and direct that part of the work.

More than this is necessary, however. As a physician first examines his patient, makes his diagnosis, then gives him the necessary treatment; so, in a campaign looking toward pure air, it is requisite to determine the nature and extent of the pollution and to ascertain the sources and causes, when the remedy in the form of regulations can be applied.

Logically, the first step is the organization of an air hygiene district, to include all parts of the smoke area, and the selection of a group to constitute an Air Hygiene Commission. The membership of this group should include representation from the medical, chemical, engineering and architectural professions; the financial, manufacturing, commercial and real estate groups, and the local government.

Survey of Atmospheric Pollution. To secure information as to the extent of pollution by products of combustion, actual measurements must be made. Some of these are direct, as the amount and chemical composition of sootfall, and the number and size distribution of air-borne solids; others are indirect, as the effect of air pollution in screening out sunshine, particularly in the ultraviolet region.

Sootfall. The collection of solid matter that falls by gravity or is brought down by rain. The smoke area is divided into districts, according to the number of stations deemed necessary to give the desired results. Naturally the greater the number of such stations, the more accurate the information as to conditions in small sections of the area. Proper containers are placed at the stations, to collect solids that fall by gravity or are brought down by rain. These collectors, when changed periodically, are conveyed to the laboratory, where the deposit can be weighed and analyzed for tar, combustible other than tar, ash, etc.

Information then will be available from which to make a dirt chart of the city, so far as sootfall is concerned, to note variations from time to time and, in connection with other data secured in ways that will be mentioned, to make comparisons as to current conditions, including health.

Air-borne Solids. There is an intermediate size range of particles that, at a fairly high wind velocity, will be carried in suspension, but at a lower wind velocity will fall. Such particles may be picked up, carried awhile and dropped, and this process repeated many times. These, with particles that are gravitating normally to the earth, and other particles so small as to remain in suspension indefinitely, are the air-borne solids which must be measured.

There are several methods of accomplishing the result. One such will give continuous record of the effect of such particles in

discoloring filter paper; another will collect an average sample over a period of time and permit microscopic study of the solids; still others are designed for instantaneous sampling, followed by determination (microscopically) of the number and size distribution of the particles. In a survey of any magnitude, a combination of these likely would be used. The last-named type has the advantage of ready portability, so that one person may take a number of widely distributed samples in a day.

Sulphur Dioxid. The concentration of sulphur dioxid, if desired, may be determined by a standard method.

Natural Sunshine. This is a free gift, to utilize which the human organism was developed through the ages. In building up his cities, man has placed a smoke and dirt screen between himself and the sun, so that he no longer receives all of the benefits to which he is entitled from the source of energy. To obtain knowledge of the extent to which this screen exists in smoky sections, compared with a clean suburb, for example, or the country, measurement of natural solar radiation is essential. The survey should include determination of the infrared, the visible and especially the ultraviolet radiation.

Due to the recent development in photoelectric cells, it is possible to secure continuous records of a part of the infrared, of the visible and of the ultraviolet radiation. For the central station and any other control stations that are set up, the records should be continuous. For readings at other stations, or elsewhere, a portable set, with indicators, can readily be devised.

Other Meteorologic Data. Temperature, relative humidity, sky conditions, rainfall, wind velocity and direction are recorded by the United States Weather Bureau. This information is available for correlation with the data from the sootfall, air-borne solids and sunshine studies.

Upon this knowledge of the amount and character of deposited and air-borne impurities to which the urban dweller is subjected, and of the amount of solar radiation, particularly in the ultraviolet, of which he is unnecessarily deprived, the physician will be able to base his advice.

This survey of atmospheric pollution is the part of the air hygiene program in which the physician will find most interest; the fact-finding is fundamental, and is necessary to show the magnitude of the nuisance and the extent to which it should be abated.

The scope, details and complexities of a study of atmospheric pollution, as outlined above and in paragraphs which follow, may not be generally understood; its necessity may not be appreciated. But, in the light of known damages and demonstrable benefits, science says the city of the future will collect regularly such information as an integral part of its public health work. Science foresees a city population which will view preventable air pollution with

the same intolerance it now displays toward water and food supply contamination.

Sources and Causes of Pollution. A survey, directed by mechanical engineers, should be made to determine the present condition of fuel-burning equipment, with special reference to its classification as: (1) Obsolete or worn out; (2) needing extensive alteration or repair; (3) requiring only minor repairs; (4) indicating change in fuel or firing method only as necessary.

There should be a comparative study, directed by engineering talent, of fuel-burning equipment and fuels offered on the local market, with a view to determining possibilities in efficiency, economy and cleanliness.

Such studies are particularly timely, because of the almost universal undermaintenance during the past 3 years, which has resulted in a country-wide need for replacement of a great deal of fuel-burning equipment and extensive alterations and repairs to much more, to prepare industrial and commercial plants for efficient operation when the present emergency ends. Then there is the vast number of heating plants that need to be replaced or repaired, or in which a different type of fuel should be used. There is an unprecedented amount of work that will have to be done to bring the plants to a condition equivalent to that before the crisis, to say nothing of making any advance toward clean air.

As information concerning conditions and needs is collected and classified, there is the opportunity to put local labor to work on the large volume of minor repairs. Major repairs and alterations can be equitably distributed among responsible local contractors. On new work, because of the information which will have been gathered by the commission, attractive prices and terms undoubtedly can be arranged.

Naturally, this is not the only plan that can be followed. It is given here in brief outline to stress the importance of a comprehensive program, to show how it may be possible to set up such standards of clean air as are feasible, and at the same time to do its part in aiding the unemployment situation and to assist owners to secure advantage of exceptional prices and terms for necessary new equipment.

Legislation. At the proper time, and in the light of the information gained in the surveys, the commission will be in position to recommend standards to be met (*a*) by new equipment, (*b*) in alterations and repairs and (*c*) by other boilers and furnaces that are currently serviceable. These standards may be embodied in an ordinance for the air hygiene district.

Economic Applications. Large-scale application of this or some similar type of campaign plan for pure air might bring economic results which would tie in with work programs that may be developed by municipal, state or federal governments.

A strong demand for fuel-burning equipment easily could step up the work schedule in a number of boiler and stoker plants where employees are idle or on part time. Even mass production might be attained and make possible the lowering of costs, especially to the domestic purchaser.

More distantly a pure air campaign would spur scientific research, which has lagged in some directions, to the task of developing yet more efficient and additional types of appliances and thus broaden the market. The perfecting and marketing of small-size dust separators would become an important industry. A wide market awaits a small stoker, priced within the reach of the "little" home owner.

Cleaner city air will be of vital assistance in the development of the air conditioning industry in smoky cities, by permitting installation of smaller and less costly systems. Currently filtration devices are made large, at consequent greater cost, to take care of "smog" conditions. Also, in smoky centers of population the filters have to be renewed or cleaned more often than should be necessary.

Real estate owners will realize what the smoke nuisance has cost them in the past, and will see the advantage in including air pollution abatement in any rehabilitation program.

Summary. We have tried to show that city dwellers have a right, as a matter of public health, to expect the standard of air purity will be brought up to a parity with that already fixed for water and food; that the rôle of leadership in this movement belongs to the medical profession; that current conditions are unusually favorable for campaign success; that a workable plan of campaign would help immediately to reduce unemployment, spur scientific research, aid infant industries and assist in the restoration of real estate values.

In conclusion, be assured that in connection with whatever action you may take you are free to call upon Mellon Institute of Industrial Research for any assistance it may be able to give, in the light of its 20 years of scientific investigation of the problems of air pollution.

THE RADIOLOGIC RECOGNITION OF HEART DISEASE IN PNEUMOCONIOSIS.

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The object of this communication is the consideration of a roentgenologic sign of cardiac disease. First, it is to be emphasized that the importance of this is not generally understood. Then, as a contribution to cardiac radiology, it will be demonstrated that

this sign may be used to diagnose specifically a pathologic heart condition caused by pneumoconiosis.

The silhouette of a normal heart, in the postero-anterior roentgenogram, presents a depression on the left border between the aortic "knob" above and the prominence of the left ventricle below. When this depressed area is replaced by a marked convexity it indicates prominence of the pulmonic artery and conus arteriosus. This fundamental observation was made by Assmann.[1] Slight prominence of the shadow may be seen in otherwise normal hearts of the hypoplastic type. When it becomes large enough to reach a line drawn from the aortic to the left ventricular prominence, it represents enlargement and serves as a sign of right ventricular hypertrophy. This is in accord with East and Bain,[2] who state that with enlargement of the right ventricle "the shadow of the pulmonary artery becomes more prominent, so that the general concavity of the left border becomes filled." Nichols,[3] in conjunction with pathologists at the Philadelphia General Hospital, has followed cases with similar cardiac silhouettes to the postmortem table, and reports the shadow to represent enlargement and hypertrophy of the pulmonic artery and the adjacent conus.

Surveys of the American literature reveal no mention of this important fact previous to 1932 when Nemet[4] stated that "such a configuration of the left cardiac contour indicates marked enlargement of the part of the right ventricle lying between the apex and the pulmonary orifice (so-called outflow tract)."

Right ventricular hypertrophy may thus be recognized in cases of mitral stenosis or congenital heart disease. According to East and Bain[2] it may be found also in emphysema. Kerley[5] notes (in quoting both Assmann and Schinz) that enlargement of the pulmonary artery may be due to certain acquired diseases which cause stasis in the pulmonary circulation, notably mitral stenosis, Ayerza's disease, and fibroid phthisis. Nemet[4] remarks that the "recognition of right ventricular enlargement is of great significance, and is the only indication of structural change of the heart in the important group of cardiac insufficiency developing in cases of long-standing pulmonary fibrosis."

Practitioners in the anthracite coal regions recognize that cardiac failure is a frequent cause of death in pneumoconiosis. A definite cardiac lesion is generally not diagnosed, however, since there is no enlargement of the transverse diameter of the heart. It is my purpose to point out that pneumoconiosis, a disease of long-standing pulmonary fibrosis, causes obliteration of much of the vascular bed in the lungs. It is reasonable to suppose that the first chamber of the heart to show reactionary change is the right ventricle. The proposition is made, therefore, that the convex shadow of the left border described above (when observed in miners with no other indication of heart disease) be regarded as evidence of right ventric-

ular hypertrophy caused by pneumoconiosis. The following cases exemplify the proposition.

Case Abstracts. CASE 1.—J. K., a white male, aged 49 years, was admitted to the White Haven Sanatorium with a provisional diagnosis of tuberculosis complicating pneumoconiosis. He complained not only of cough and expectoration but also of swelling of the ankles. He had been a miner for 27 years and had used the jack-hammer for 5 years. Observations made by Dr. Ross K. Childerhose of the sanatorium staff at that time (1931) included: "Temperature was always normal. He was 12 per cent underweight, and had slight cardiac decompensation. There was moderate cough with 3 fluidounces of expectoration daily. Eighteen sputum examinations were negative for tubercle bacilli as well as two 24-hour collections for concentration and culture methods." In August, 1932, he was brought to the Hazleton State Hospital for study. There was no history of rheumatism or syphilis. Physical examination was negative except for moderate emaciation and a fairly loud to and fro murmur over the pulmonic area. Blood Kahn test was negative. A roentgenogram made at this time was no different from that made at White Haven which disclosed pneumoconiosis, shadows suspicious of tuberculosis, and enlargement of the pulmonary artery and conus shadow. Electrocardiographic examination showed right axis deviation (Fig. 1).

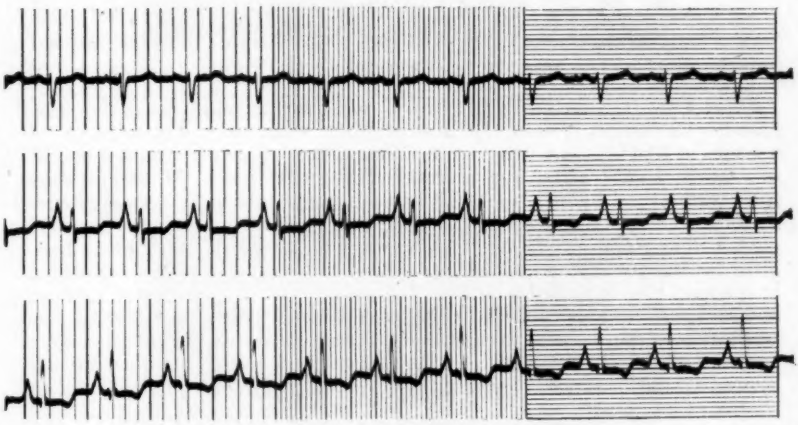

FIG. 1.

Comment. The roentgenogram (Fig. 2) shows no enlargement of the transverse diameter of the heart. The sign of right ventricular hypertrophy can be demonstrated quite definitely, however.

CASE 2.—A. G., a frail white man, aged 51 years, a miner for more than 30 years, admitted to the medical service on September 21, 1931, presented weakness of the arms and legs, in addition to cough, expectoration and substernal pain. Physical examination showed a rapid but regular heart action. Cardiac sounds were "distant and diminished in intensity." Fine râles were heard in each base. Moderately advanced arteriosclerosis was present. No other observations were remarkable except the neurologic examination which disclosed progressive spinal muscular atrophy. Laboratory findings, including blood and spinal fluid Kahn tests, were normal.

Roentgenologic examination showed third stage pneumoconiosis and a very prominent pulmonary artery and conus shadow. This man left the hospital against advice 4 days later, and died at home in April, 1932. No electrocardiogram was obtained.

Comment. The roentgenogram (Fig. 3) confirmed the clinical impression of heart disease.

CASE 3.—M. F., a white male, aged 52 years, came to this hospital in September, 1932, with symptoms of cough, dyspnea, and swelling of the ankles, worse in the last 2 weeks. He had worked in the mines for 10 years, and had handled the jack-hammer for more than 1 year. There had been no rheumatic symptoms, no tonsillitis, and no venereal infections in his past history; his wife had had 6 children (5 living and well) and no miscarriages. There were no other noteworthy facts in his history. Physical examination revealed dyspnea, slight enlargement of the area of cardiac dullness to the right, exaggeration of the pulmonic second sound, râles in each base, and edema of the ankles. Blood Kahn test was negative. Roentgenologic chest examination reported third stage pneumoconiosis and hypertrophy of the right ventricle of the heart. Right axis deviation was found on the electrocardiogram (similar to Fig. 1 and Fig. 6). This man, slightly relieved by hospitalization, returned to his home and is still living.

Comment. Right-sided hypertrophy here (Fig. 4) has not only "filled out" the left border of the cardiac silhouette but has caused enlargement of the transverse diameter to the right.

CASE 4.—J. G., aged 45 years, was a miner for 26 years, using the jack-hammer for the last 7 years. Because of cough, weakness and blood streaked sputum he had been admitted to the White Haven Sanatorium for a month in August, 1932. There was no fever during that time. Moist crackling râles were found in the lower half of each lung, as well as extensive consolidation in the upper halves. Eleven sputum examinations were negative for tubercle bacilli. In October, 1932, he came to the Hazleton State Hospital because of distressing cough, expectoration and anorexia. Nothing in his past life suggested syphilis or rheumatic fever. Prominent findings included emaciation, copious thin expectoration, marked decrease of respiratory excursions, loud moist râles throughout the chest, and an accentuated pulmonic second sound. Urinalyses and blood counts were not abnormal, and the Kahn test proved negative. Roentgenologic studies showed third stage pneumoconiosis and a cardiac shadow suggestive of pulmonary artery enlargement. Electrocardiography produced a tracing of right axis deviation (similar to Fig. 6). After 2 weeks' hospitalization during which he received insulin and the high caloric régime advocated for emaciation, this patient gained 6 pounds and improved enough to be discharged to the dispensary.

Comment. Fluoroscopy demonstrated the pulmonary artery prominence more conclusively than the roentgenogram (Fig. 5). The reactionary enlargement of this structure here might be caused by the drag of adhesions as well as decrease in the pulmonary vascular bed. This would be in agreement with Dietlen,[6] who cites as a case in point chronic pulmonary tuberculosis with fibrotic lung tissue dragging on the pulmonary artery. Kerley,[5] and Pancoast and Pendergrass[7] also admit of this possibility.

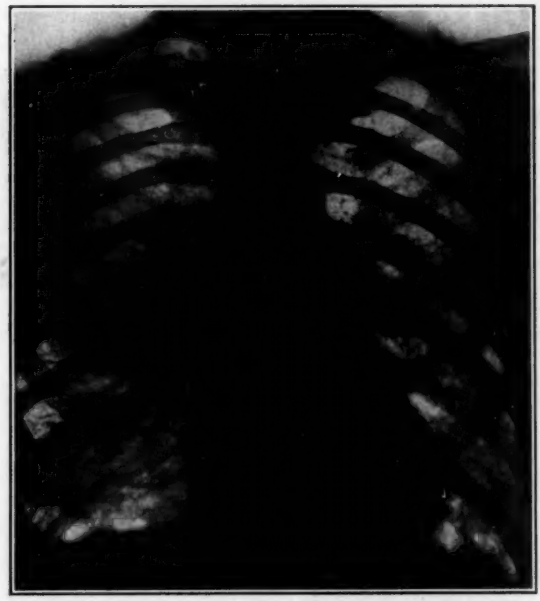

FIG. 2.—Case 1. Roentgenogram shows difficulty of excluding tuberculosis. Left cardiac border presents prominent shadow of the pulmonary artery and conus.

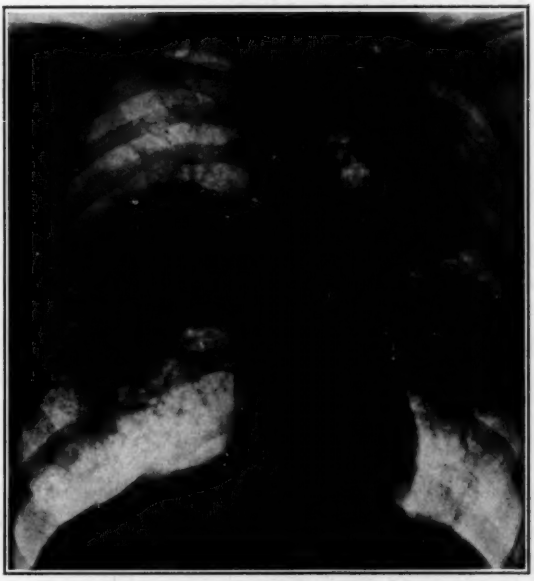

FIG. 3.—Case 2. Roentgenogram taken September 22, 1931. In addition to the pneumoconiosis the shadow on the left border of the heart is clearly seen.

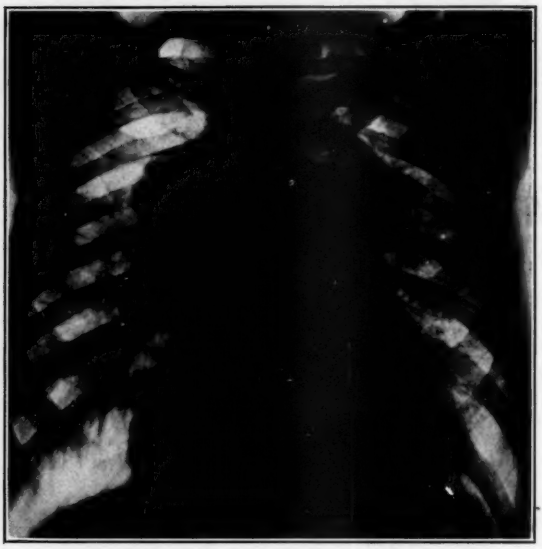

FIG. 4.—Case 3. The left cardiac border is filled out. Right ventricular hypertrophy.

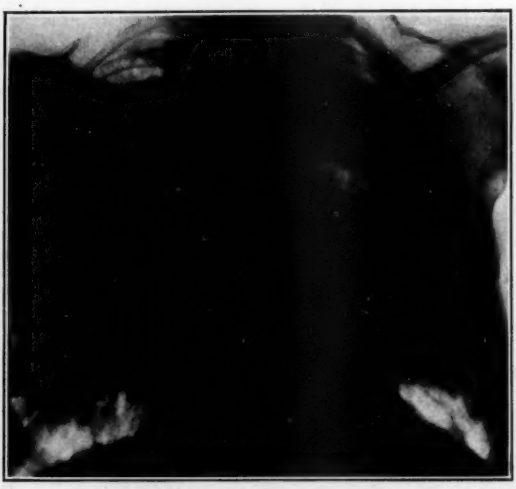

FIG. 5.—Case 4. No enlargement of the transverse diameter of the heart. Pulmonary artery and conus prominence indicate reaction of the right heart to the marked pneumoconiosis.

CASE 5.—H. C., a white male, aged 43 years, was referred to this hospital in October, 1932, for gastro-intestinal studies. His presenting symptoms of diarrhea and lower abdominal discomfort were of only 2 weeks' duration. He had suffered, however, with cough, dyspnea and some dysphagia for 6 months. These were becoming worse instead of better. For 17 years he had worked in the mines, and for 6 months had used rock drills and jack-hammers. He had never had rheumatism, tonsillitis or syphilis. Three children are living and well and his wife had had no miscarriages. Physical examination disclosed nothing remarkable other than limited respiratory excursions, evidence of fibrosis in the upper lobes, and loud, coarse râles throughout the bases. Laboratory studies including the Kahn test were negative. Roentgenologic study of the chest showed third stage pneumoconiosis, most marked in the upper halves of each chest, and a cardiac silhouette indicative of pulmonary artery and conus prominence. An electrocardiogram was made which showed no abnormalities except right axis deviation. After these examinations were completed the patient returned home. No organic disease of the stomach or intestines could be demonstrated.

Comment. The roentgenogram is similar to Fig. 5. The electrocardiogram (Fig. 6) shows the same feature observed in Cases 2, 3 and 4: inversion of the main deflection of the *Q–R–S* complex in Lead 1.

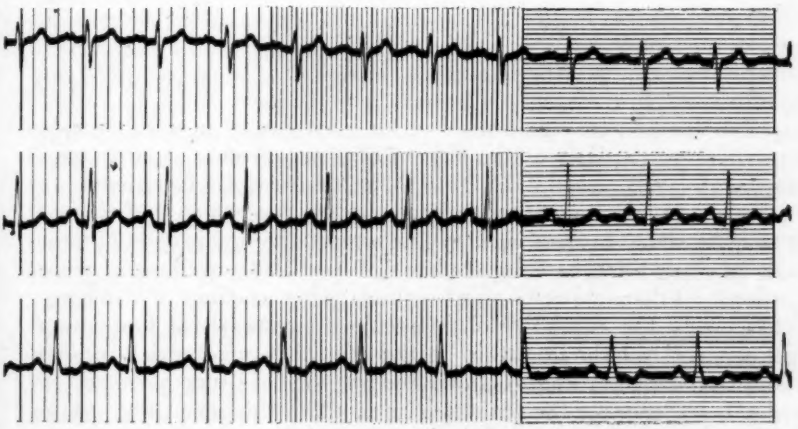

FIG. 6.

Summary and Conclusions. 1. The roentgenologic sign of hypertrophy of the pulmonary artery and the right ventricle is described, and its importance emphasized.

2. Five cases, with their roentgenograms, are presented to demonstrate how this sign may be utilized to diagnose right ventricular hypertrophy due to pneumoconiosis. Electrocardiograms were made in 4 of these cases, each of which presented right axis deviation.

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THE HEALING OF TUBERCULOUS CAVITIES: A CLINICAL STUDY.*

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The prognostic significance of an open cavity in a tuberculous patient, particularly at the time of discharge from a sanatorium, is generally recognized. In 1916 King[1] showed that patients discharged from Loomis Sanatorium with sputum which had changed from bacillary to non-bacillary had a mortality at the end of 5 years of 225 per 1000, as compared to 710 per 1000 of those in whose sputum tubercle bacilli were demonstrable at time of discharge. Obviously the curability of tuberculous cavities is of first importance, and yet the literature on the subject is replete with conflicting views. According to Gräff,[2] the presence of cavity portends the death sentence for the patient. He modifies this remark by stating that this sentence frequently is not carried out for several years. Barnes and Barnes,[3] in a study of 1454 tuberculosis cases with cavity found a mortality of 80 per cent within 1 year. In contrast with this figure Fales and Beaudet,[4] in 120 cases with cavity, reported 48 (40 per cent) healed spontaneously. These cases represented 147 cavities, 62 (42 per cent) of which healed. Fischel[5] found that, in those cases receiving institutional care but no other form of treatment, results were so disappointing that he concluded that the existence of pulmonary cavity in poor patients calls for a more

* Paper read before the American Sanatorium Association (Eastern Section) at Waltham, Mass., October 14, 1932.

active therapy, the aim of which should be the obliteration of cavities before the patient is discharged.

In order to reconcile these conflicting and extreme views, and to determine, if possible, significant prognostic factors as to the curability of cavity, a detailed study was made of 296 cases with tuberculous pulmonary cavities at Loomis Sanatorium.

Plan and Scope of Study. Only those cases were included in this study that had cavity demonstrable roentgenographically and tubercle bacilli in the sputum. The minimum period of our observation was 3 months, the shortest period considered to be sufficient to establish at least a trend in the course of the disease. There were but few, however, in this minimum observation group, the average period of observation of the whole group being about 13 months. Cases were taken consecutively from the files of Loomis Sanatorium over a period of 3 years (1928 to 1931); of the 800 cases examined only 296 fulfilled the criteria for inclusion. The following factors were recorded in each case: age, sex, period of observation, side of lesion, size and location of cavity as observed on stereoscopic P. A. Roentgen rays, type of cavity wall and nature of surrounding infiltration; estimate from the history of the duration of the disease and cavity; the amount and bacillary content of the sputum; constitutional reaction (temperature, pulse rate, toxemia); complications; status of body weight as compared with standard; diagnosability of cavity from physical signs and changes in physical signs; duration of bed rest and exercise. Notation was made of the significant changes in the serial Roentgen rays and all the above factors correlated for that particular time. The induction of collapse therapy was indicated and progress thereafter reported.

Since it is of primary importance to determine what actually can be expected in the way of spontaneous healing of cavities, the 296 cases were first classified according to the criteria listed below. If they received no collapse therapy this classification was final. If they received collapse therapy they were classified first on the basis of the changes that had occurred spontaneously and then again to show the results of collapse therapy. In order to avoid confusion in cases receiving collapse therapy soon after admission, an arbitrary time limit of 2 months was set, and all cases receiving collapse therapy within this short period were classified in a separate group, the *Early Collapse Therapy* group, according to the result of this therapy. Thus we have an initial classification arrived at on the basis of spontaneous healing, plus the "early collapse therapy" group, and final classification after adding in the results of later collapse therapy.

The criteria for the initial, and for our purpose most important, classification were as follows: 1, *Spontaneous closure*—sputum negative on concentration for at least 3 months; the shadows representing cavity to be no longer present on the Roentgen ray. 2, *Much*

improved—marked shrinkage in size of cavity, which should not exceed 1 by 1 cm.; sputum negative or positive. 3, *Slightly improved*—total cavity reduced in size, but in excess of 1 by 1 cm. 4, *Unimproved*—Roentgen ray and pathologic anatomy substantially unchanged or worse, irrespective of clinical improvement. Clinical improvement as evidenced by gain in weight, reduction or disappearance of fever was recorded, but did not influence the final classification. Thus, according to the American Sanatorium Association, a patient might be classified as *quiescent*, but in our study would be *unimproved* because of the essentially unchanged pathologic anatomy.

TABLE 1.—RESULTS OF TREATMENT BY BED REST ALONE AND AFTER COLLAPSE PROCEDURES.

	Results of treatment by bed rest alone (spontaneous healing).	Received collapse therapy after observation.	Results of collapse therapy.		Final results, combining spontaneous healing with collapse therapy.
			Cavity closure secured.	Other changes in status.	
Cavity closure secured	65*= 22%	....	....	.....	115 = 38.8%
Much improved	38 = 13%	3 { 1 P 2 Ph	2 { 1 P 1 Ph	1 remained much improved	72 = 24.3%
Slightly improved	47 = 15%	23 { 8 P 12 Ph 1 P+Ph 2 Th	8 { 1 P 5 Ph 2 Th	6 became much improved 9 remained slightly improved	53 = 17.9%
Unimproved	84 = 28%	57 { 39 P 17 Ph 1 Ph+Th	13 { 10 P 3 Ph	18 became much improved 9 became slightly improved 17 remained unimproved	56 = 18.9%
Given early collapse therapy (No preliminary observation)	62 = 21% 54 P 8 Ph		27 { 20 P 3 Ph 1 Ph+P 3 P+Th	12 became much improved 11 became slightly improved 12 were unimproved	

* All figures refer to cases, not individual cavities.
P = received therapeutic pneumothorax; Ph = received phrenicectomy; Th = received thoracoplasty.

Application of these criteria for classification gives us the figures of Table 1. The 296 cases, classified according to the Sanatorium Association classification, were divided into 36 per cent "moderately advanced" and 64 per cent "far advanced." The number and percentage of the 5 major groups are shown first. There were 65 cases (22 per cent) in the spontaneous closure group. To make the study complete the subsequent course of the other groups and the influence of collapse therapy on their final status, is indicated. The question may be raised: Why did not more (only 3 of 38) of the "much improved" group later receive collapse therapy, in contrast with the "slightly improved" and "unimproved" groups, of whom 50 and 60 per cent respectively, received collapse therapy?

The reason is that these patients were too well for such therapy and from their past favorable progress it was reasonable to anticipate spontaneous closure. Of the 23 first classified as "slightly improved" and then receiving collapse therapy, 33 per cent obtained closure. Of the 57 first classified as unimproved prior to collapse therapy, 22 per cent obtained closure. Of all who received collapse therapy in these groups 24 per cent obtained closure. Of the 63 in the "early collapse" group, 37 per cent obtained closure and an additional 6 per cent by supplementary surgical procedures. Summing up the results obtained in the whole group shows 65 (22 per cent) obtaining closure spontaneously and 50 (17 per cent) obtaining closure as the result of different forms of collapse therapy. Thus a total of 115 (39 per cent) of the 296 cases eventually were classified as arrested disease.

The markedly higher percentage of closure recorded for the early pneumothorax group (37 against 24) immediately attracts attention and demands explanation. The answer, after analyzing the cases in the two groups, appears to be that it is rather the type of case than the early collapse that gives a higher percentage of closure in the early collapse group. Of 54 early pneumothorax cases, only 4 (7 per cent) had excavation in the contralateral lung, while in the later group of 50 cases, 26 (52 per cent) had cavity in the so-called "good lung." In many instances in the latter group, pneumothorax was withheld until healing changes were demonstrated in the contralateral lung. In others pneumothorax was given in spite of obviously unhealed or unhealing cavities in the hope of obtaining benefit from control of the main focus of disease. In several cases bilateral pneumothorax was given.

Analyses of Factors Influencing Healing. *Side of Cavity.* The frequency of right to left to bilateral cases was 42 to 27 to 31. In this series the incidence of cases with cavity only on the right was definitely preponderant. Furthermore, in considering the 65 cases which satisfied the criteria for spontaneous closure, the incidence of healing was greater on the right—more than twice that of left-sided and three times that of bilateral cases. While this series is too small to draw conclusions from these figures, it is felt that at least a trend is indicated in favor of the right side.

Sex. In the group studied there were 170 men and 126 women. Practically the same percentage of both sexes appeared in the spontaneous closure group and in the unimproved group. It is felt, therefore, that in any large group the factor of sex plays very little part.

Age. In considering age and sex together, however, particularly in different age groups, significant deviations from the average are noted in the percentage of spontaneous closure and of unimproved. The per cent of spontaneous closure for the whole group was 22. Under 25 years, the percentage chance of spontaneous closure was

17. Under 20 the percentage chance of closure for girls was even more significantly less, namely, 11 per cent. Furthermore, the percentage of unimproved was highest in girls under 20 (64 per cent *versus* 28 per cent average). Significant deviation from average in unimproved was also noted in the age group over 45, where a percentage of 40 (*versus* 28 average) was recorded. In other words, resistance to tuberculosis appears to be lower in middle age and adolescence, particularly in young girls.

Average Period of Observation. The spontaneous closure group had the shortest average stay (10.6 months). This figure showed increase in the other groups up to 15.9 months as a maximum in the unimproved group. In other words, in terms of the average, the closure group did well fairly quickly, and length of stay in the other groups was longer in proportion to severity of disease and poor resisting powers. The figure for the early collapse group (11.6 months) is comparatively low, and may be explained by the fact that a number of this group returned home after getting a stable pneumothorax, and obtained refills there. As closely as could be estimated, the average length of time for spontaneous closure by our criteria was 5.6 months. This figure is of interest in comparison with the average time for closure in successful pneumothorax cases (5 to 6 months) as reported by Herben and Franklin* in a study of therapeutic pneumothorax at Loomis Sanatorium.

The Age of Cavity. This cannot be estimated accurately from the history. In this study cavity was considered present from the date of the first hemoptysis or first bacillary sputum or appearance of suggestive cough and expectoration. Using these criteria, the average age of cavity for the closure and unimproved groups was, respectively, 5.4 months and 11.1 months, figures roughly proportional to the number of heavy-walled cavities in these groups.

Body Weight. Increase in body weight is usually a favorable sign, but not always so. As a general rule, patients and the laity place more emphasis on it than on any other single symptom. The status on admission of the 296 cases was: 39 (13.1 per cent) above standard, 249 (84.1 per cent) below and 8 (2.7 per cent) standard weight. At the end of the period of observation, 227 (76.6 per cent) had gained weight, 62 (20.9 per cent) lost and 7 (2.3 per cent) remained stationary. Analysis of changes in body weight in groups according to final status showed, in the closure group of 65 cases, 56 (86.1 per cent) gained weight, 6 (9.2 per cent) lost and 3 (4.6 per cent) remained unchanged. In the unimproved group of 83, 51 (61.4 per cent) gained, 31 (37.3 per cent) lost and 1 (1.2 per cent) remained unchanged. Estimating progress from gain in weight alone the factor of error is considerable, *viz.*, 61.4 per cent in the unimproved group and 20.9 per cent in the closure group. An interesting finding was that the greatest percentage of cases above

* To be published.

standard on admission was in the group finally classified as unimproved. This shows that being overweight at start of treatment is not an index of subsequent progress.

Toxemia. As indicated in the introduction, temperature reaction was recorded on admission and subsequently in each case. The percentage of cases febrile on admission in the various groups of our classification was: spontaneous closure, 18 per cent; much improved, 23 per cent; slightly improved, 48 per cent; unimproved, 52 per cent; early collapse, 85 per cent. There was a striking parallel between these figures and the percentage of cases with heavy infiltration in the various groups. The high incidence of fever in the early collapse group was one of the chief reasons why a preliminary period of observation was eliminated in that group.

Complications. Tuberculous complications had an increasing incidence as the final status was more unfavorable, ranging from 6 per cent for the spontaneous closure group to 30 per cent for the unimproved group. There was no such correlation in the incidence of nontuberculous complications. Twenty-one per cent of the 296 cases had tuberculous and 5 per cent nontuberculous complications.

Treatment. In recording the kind of treatment received, it was of interest to note that the average duration of bed rest paralleled the severity of the disease (3.6 months in the closure group to 10.1 in the unimproved group). The influence of prolonged bed rest in securing healing could not be accurately determined because there are no controls. In individual cases, as the study was made, significant episodes were observed which tended strongly to strengthen our impression of the importance of adequate initial bed rest. The average duration of bed rest for the early collapse group (7 months) was about twice that of the spontaneous closure group.

Sputum. The fluctuations in the amount and bacillary content of the sputum were found important in individual cases, but were factors difficult to generalize. They are usually proportional to the severity of the disease, but not infrequently there may be little secretion from a large cavity or the patient may be swallowing the sputum, while associated with a small cavity there may be considerable expectoration, either because the patient is sputum conscious, or because there is a secondary complication, as chronic sinusitis. Average figures for 2 by 2 cm. cavities in the closure and unimproved groups were: 10 gm. of Gaffky III (average 1 bacillus in each microscopic field) and 15 gm. of Gaffky IV (average 2 to 3 bacilli in each field), respectively. For 4 by 4 cm. cavities, corresponding figures were: 10 gm. of Gaffky IV and 16 gm. of Gaffky IV. It is observed that the average figure gives very little information, even in the order of a trend.

Factors Revealed by Roentgen Ray. Finally, and probably most important, are factors revealed by the Roentgen ray. Of the whole group there were 24 per cent who during observation had Roentgen

ray evidence of extension of their disease. (This figure does not take into account increase in size of cavities already present, but represents new disease.) The spread was commonest on the same side, then both sides, then the opposite side. The percentage of spread of the early collapse group was 25, practically identical with the group as a whole, and here the order of frequency was opposite side, same side, both sides. The incidence shows an increase from 13 per cent for 2 by 2 cm. cavities to 29 per cent for cavities over 4 by 4 cm.

Extent of Excavation. Table 2 shows an analysis of the 296 cases according to total diameter of cavities as revealed by the Roentgen ray. Prognostic information of value is immediately apparent. Where the extent of excavation was not over 2 by 2 cm., 48 per cent of the cases healed spontaneously. With excavation totalling not over 3 by 3 cm., this figure dropped to 21 per cent for the group, while in the other two groups (4 by 4 and over 4 by 4 cm.) the figures were 15 and 7 per cent, respectively. Furthermore, the percentage of unimproved showed increase with the extent of excavation. There was little difference in the 2 by 2 and 3 by 3 cm. groups (20 per cent), but thereafter the figure jumped to 35 per cent. Early collapse therapy was infrequent in cavities up to 2 by 2 cm. (9 per cent), but was indicated two and three times as often in subsequent groups.

TABLE 2.—RESULTS ACCORDING TO EXTENT OF EXCAVATION.

Total diameter of cavities.	Spontaneous closure.		Much improved.		Slightly improved.		Unimproved.		Early collapse therapy.		Totals.
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
2 by 2 cm. .	34	48	7	10	9	13	14	20	6	9	70
3 by 3 cm. . .	13	21	11	19	13	20	11	19	12	20	60
4 by 4 cm. . .	10	15	8	12	9	14	22	34	15	23	64
Over 4 by 4 cm.	8	7	12	11	16	15	37	36	29	28	102
Totals . .	65	..	38	..	47	..	84	..	62	..	296

Table 3 shows the results of a study of the total 464 cavities from the point of view of size, location, heaviness of surrounding infiltration and type of cavity wall. It should be pointed out that further subdivision into pathologic types is not indicated. While undoubtedly it is important in any individual case to decide whether we are dealing fundamentally with caseous or fibrous disease, for statistical purposes it seems sufficient to record our findings in the terms indicated in the table.

TABLE 3.—FACTORS INFLUENCING HEALING.

Size of cavity.		Size.	Location.			Surrounding infiltration.			Cavity wall.			
			Peripheral.	Central.	Medial.	Slight.	Moderate.	Heavy.	Thin.	Moderate.	Thick.	Honeycombed.
2 by 2 cm.	Number of cavities	81	38	34	9	3	41	37	19	11	7	44
	Per cent spont. closure	40	31	52	22	66	51	25	52	36	28	37
3 by 3 cm.	Number of cavities	78	37	39	2	6	36	36	23	12	2	41
	Per cent spont. closure	20	21	25	0	33	19	17	26	17	0	19
4 by 4 cm.	Number of cavities	97	55	35	7	9	45	43	40	16	4	37
	Per cent spont. closure	13	16	17	15	22	19	9	20	12	0	8
Over 4 by 4 cm.	Number of cavities	208	122	77	9	12	56	140	72	30	26	70
	Per cent spont. closure	6	4	6	10	16	14	3	8	3	0	5
	Number of cavities	464	252	185	27	30	178	256	154	69	39	202
	Per cent spont. closure	17	12	22	15	27	22	9	20	13	5	14

The factors named above are doubtless subject to variation with individual interpretation, but since they were recorded uniformly they may be considered suitable for study. The location of cavity, recorded as peripheral, central or medial, upper, middle, or lower third, was determined by stereoscopic Roentgen rays, by fluoroscopy, or by both methods. Surrounding infiltration was denoted as slight, moderate or heavy. The cavity wall was described as thin, moderately thick, thick or honeycombed. The size of honeycombed cavities was estimated according to the extent of the diseased area involved.

Size of cavity is again shown to be important in healing prognosis. Other things being equal, the location of cavity in the lung definitely influences the chances for spontaneous healing. In cavities of all sizes central location was more favorable than peripheral. A medial location is least frequent, but is seen to be more favorable than peripheral in our series.

The nature of the infiltration surrounding a cavity is an extremely important factor in influencing healing. The table shows clearly that the incidence of healing with slight surrounding infiltration is high, while with heavy infiltration it is very low, and the patient is likely to be in the unimproved group. The incidence with moderate surrounding infiltration is higher than midway between the two extremes.

Furthermore, as has been frequently recognized, the type of cavity wall has prognostic significance. It is demonstrated in Table 3 that cavities described as having a thin wall have the best chance for spontaneous healing, while those with a moderate wall have 35 per cent less chance. Cavities with definitely thick wall

do very poorly, and in such cavities over 2 by 2 cm. spontaneous healing was not recorded. Honeycombed cavities occupy an intermediate position, but in general their prognosis was below the average for the group. It is difficult to determine closure satisfactorily in this type of cavity, for not infrequently changes interpreted as honeycombing, which may possibly be due to emphysematous blebs, will still be present on the Roentgen ray after the sputum is negative on concentration.

Comment. From the above findings the necessity for individualization in the treatment of pulmonary tuberculosis with cavity is demonstrated. The presence of cavity undoubtedly constitutes a serious menace, but before instituting collapse therapy all factors should be carefully weighed; and if they are not highly unfavorable, a preliminary period of observation with the patient at bed rest is fully justified. The danger of spread of the disease during such a period has, except in acute cases, been overemphasized. In this study, of those who had extension of their disease 85 per cent were febrile at the time of spread. From this it may be inferred that, if the patient is afebrile and doing well clinically at bed rest, there is not much danger of spread. Furthermore, collapse therapy does not eliminate this danger, as is shown by the fact that the early collapse group had a 25 per cent incidence of spread after collapse, as compared with 24 per cent for the group as a whole, which contained many hopeless cases. If it is apparent that spontaneous healing is taking place, the bed rest program should be continued with fluoroscopic examination at intervals of not longer than 2 weeks and Roentgen rays at intervals of not longer than 1 to 2 months. If these observations do not reveal satisfactory progress, collapse therapy is indicated. As to the likelihood of the development of obstructive and troublesome adhesions between the layers of the pleura during the preliminary period, there is no positive evidence that such is the case. It is rather the type and distribution of the lesion with involvement of the pleura and not necessarily the duration of the disease which determines whether adhesions will be present. Packard[6] has shown that a good collapse by pneumothorax may at times be brought about in cases of long standing with extensive retraction. At Loomis, several instances have been observed in which there developed, apparently simultaneously with acute extension, surface adhesions directly over and limited to the newly involved area. Without denying the value of collapse therapy there are a number of reasons why spontaneous healing, when it can be obtained, is the most desirable form of healing. First, there is the time element. In this series the average time for spontaneous closure was 5 to 6 months. According to Herben and Franklin, the average time for closure by pneumothorax in cases where this desirable result was brought about was 5 to 6 months; and it must be remembered that this is merely the starting

point, for the lung must usually be kept down at least 2 years and then reëxpanded. Furthermore, the average duration of sanatorium residence for the early collapse group was 11½ months, compared with 10½ months for the spontaneous closure group, and the average period of bed rest for these groups was 7 months and 3½ months, respectively. In addition, collapse therapy is not without its risks. In prescribing pneumothorax, the fact is frequently overlooked that complications are the rule rather than the exception. Tuberculous pleuritis complicating therapeutic pneumothorax is very frequent; this is at times so severe as to cause, by reason of pleural thickening and ingrowth of fibrous tissue from the pleura, permanent loss of function of the lung, and necessitate thoracoplasty. In the average pneumothorax case the damage to the lung is out of proportion to the extent of the disease, and marked retraction on reëxpansion is frequent. That these objections, however, did not, in our estimation, constitute contraindications, especially when the disease failed to heal or was progressive, is shown by the fact that 49 per cent of the 296 cases received some form or combination of forms of collapse therapy during residence.

Summary. A study of 296 cases of pulmonary tuberculosis with cavity (464 cavities) at Loomis Sanatorium showed the following: Classified as to extent of excavation, there were 23.6 per cent with cavity, 2 by 2 cm.; 20.1 per cent, 3 by 3 cm.; 21.6 per cent, 4 by 4 cm., and 34.4 per cent over 4 by 4 cm. Of the whole group 22 per cent secured spontaneous closure of cavity. The chance for spontaneous healing was inversely proportional to the size of the cavity. Closure occurred in 40 per cent of 2 by 2 cm. cavities, 20 per cent of 3 by 3, 13 per cent of 4 by 4, and 6 per cent of over 4 by 4.

Where the infiltration surrounding the cavity was slight, the percentage of spontaneous closure was higher for cavities of all sizes. The heavier the surrounding infiltration the less the chance for closure to a minimum of less than half the average for cavities with heavy surrounding infiltration. Similar relations pertain in considering the thickness of the cavity wall: thin-walled cavities of all sizes, especially with slight surrounding infiltration, do better than the average. The thicker the wall the poorer the chance for healing to a minimum of 5 per cent for thick-walled cavities.

Central location gives twice as good a healing prognosis as peripheral, that is, close to the parietal pleura. Right-sided cavities in this series had twice the percentage of spontaneous closure of left-sided and three times that of bilateral cavities.

The age group 15 to 25 did only about 50 to 75 per cent as well as the average in spontaneous healing, and had a large number unimproved (45 per cent *versus* 25 per cent average). In girls aged under 20 years only about half (11 per cent) the average secured spontaneous closure and the per cent unimproved was 64. Over 45 years there was a high percentage unimproved (40 per cent).

Gain in body weight is shown to be an unreliable index of healing, since 60 per cent of the unimproved gained weight.

The incidence of spread for the whole group, which included many hopeless cases, was 24 per cent. In the early collapse therapy group, the incidence of spread was the same.

Classification made on the basis of spontaneous healing (except for 22 per cent in the early collapse therapy group) showed 22 per cent spontaneous closure, 13 per cent much improved (cavity reduced to a remnant; sputum positive or negative), 15 per cent slightly improved, and 28 per cent unimproved.

Sixty-five per cent of the unimproved, 50 per cent of the slightly improved and 7 per cent of the much improved received collapse therapy. All of these constituted 27 per cent of the 296 cases. Thus, a total of 49 per cent of the group received some form or combination of forms of collapse therapy, and roughly one-third, or 17 per cent, secured cavity closure thereby.

Finally, using all forms of treatment in 296 cases with cavity, an excellent result was obtained in 39 per cent (closure), and a good result in an additional 25 per cent (much improved).

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INCIDENCE OF RHEUMATIC FEVER IN NEW YORK CITY HOSPITALS.*

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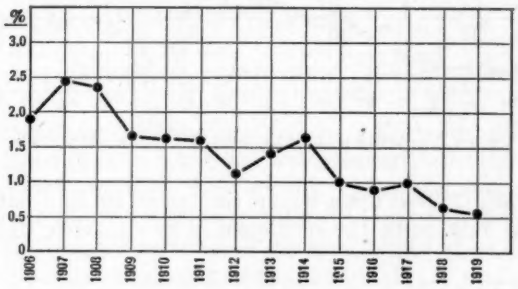
It has been noted by a number of physicians that there were fewer cases of rheumatic fever on the wards in the general hospitals after the World War than there had been previously. The present survey was undertaken to determine the truth of this statement as well as the underlying cause. It was hoped to obtain some information concerning the incidence of the disease and the effect of various conditions, such as the removal of infection, on the morbidity of rheumatic fever in this city.

Such an investigation is necessarily fraught with many difficulties and inaccuracies. The change of fashion as to what constitutes

* Read before the Medical Section of the New York Academy of Medicine, May 17, 1932.

a diagnosis of acute rheumatic fever, the ever changing house staff and attending staff, and the incompleteness of records in the early days, are some of the points which must be considered before reaching a conclusion. In order to minimize the errors due to the first difficulty, *i. e.*, the difference in terminology of diagnosis, the charts of all the cases diagnosed as acute rheumatic fever, acute polyarthritis and acute arthritis have been examined. Only those cases were included in this series which had fever and an inflammatory arthritis affecting two or more large joints and usually showing cardiac manifestations. It was also thought that limiting the study to two hospitals, where the respective attending staffs had been present for a rather long period, would further minimize this difficulty.

Similar studies have already been reported by many other investigators, but the results are not in agreement. Alexander Lambert[1] published a paper in 1920 on the incidence of acute rheumatic fever

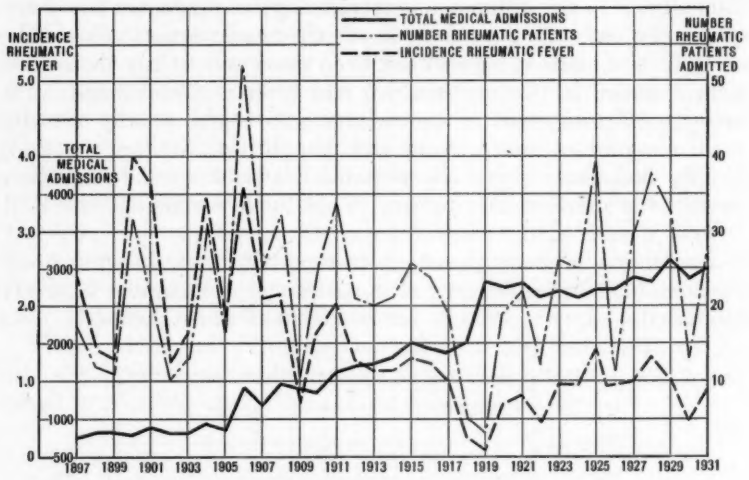


GRAPH 1.—Incidence of acute rheumatic fever.

at Bellevue Hospital. He reviewed the data of the cases from 1906 to 1919 and called attention to the steady decline in the number of cases. This decline, which is illustrated in Graph 1, was attributed by Lambert to the increasing removal of foci of infection, particularly due to the prevalence of better dental hygiene.

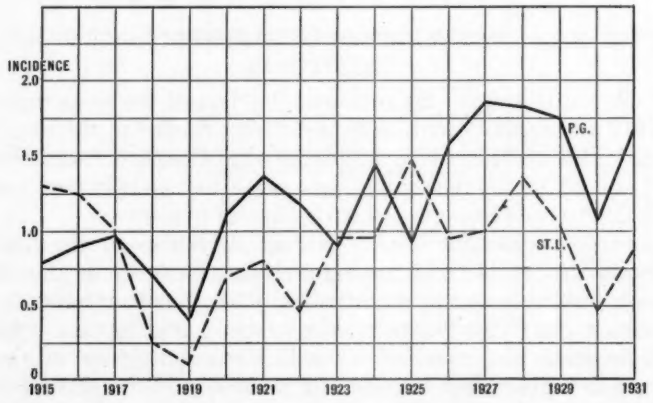
Poynton[2] began his book, "Recent Advances in the Study of Rheumatism" (1931) by saying "rheumatic fever in the clinical form would seem to be on the wane." On the other hand, in 1924 Ingerman and Wilson[3] concluded a paper by stating that "the general progress in preventative medicine and hygiene in the last twenty-five years has not seemed to influence the clinical course of rheumatism as we see it today." The latter investigators studied 185 cases of rheumatic fever, 88 per cent of which had their tonsils removed. Recurrences of rheumatic manifestations were observed in 75 per cent of the tonsillectomized patients in from 1 to 11 years. In the control group of 97 cases studied over a similar period, 80 per cent showed recurrence of rheumatic manifestations.

Kaiser,[4] however, throws a ray of hope into that dark outlook. In his investigation, 48,000 school children were divided into two groups; 20,000 who had had their tonsils removed at least 5 years



GRAPH 2.—Acute rheumatic fever (St. Luke's Hospital).

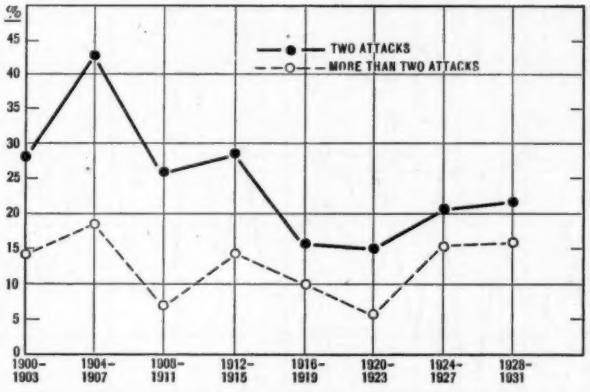
previously and 28,000 upon whom the operation had not been performed. At first sight the incidence of rheumatism did not seem



GRAPH 3.—Incidence of acute rheumatic fever (Post-Graduate and St. Luke's Hospitals).

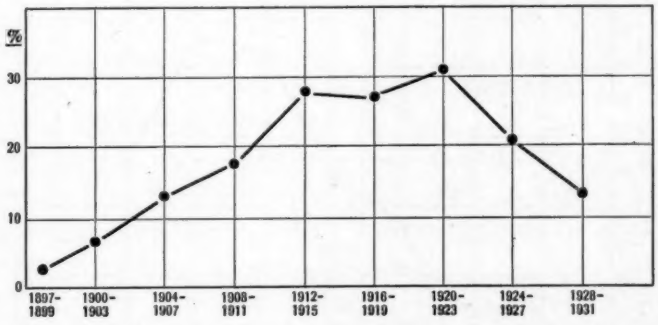
to be much influenced by the operation, since it occurred in 8 per cent of the tonsillectomized children and in 10 per cent of the non-tonsillectomized. Recurrent attacks of rheumatic fever, however,

were decidedly less common in the group who had had their tonsils removed and the incidence of carditis following chorea was also definitely diminished.



GRAPH 4.—Incidence of recurrent attacks (St. Luke's Hospital).

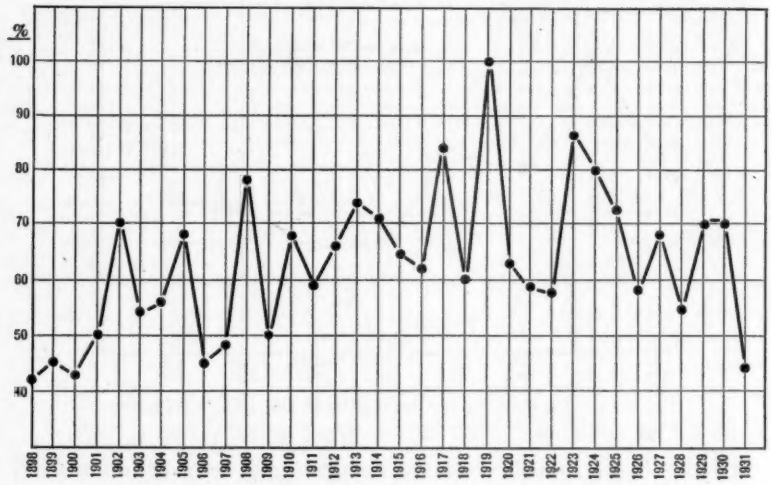
Of the 20,000 tonsillectomized children, 450 were suffering from rheumatic heart disease, while 817 were similarly affected among the 28,000 who still retained their tonsils. More significant was the discovery that in 478 cases of carditis the condition had developed in 83 per cent before operation, whereas it appeared as a first manifestation after enucleation of tonsils in only 179.



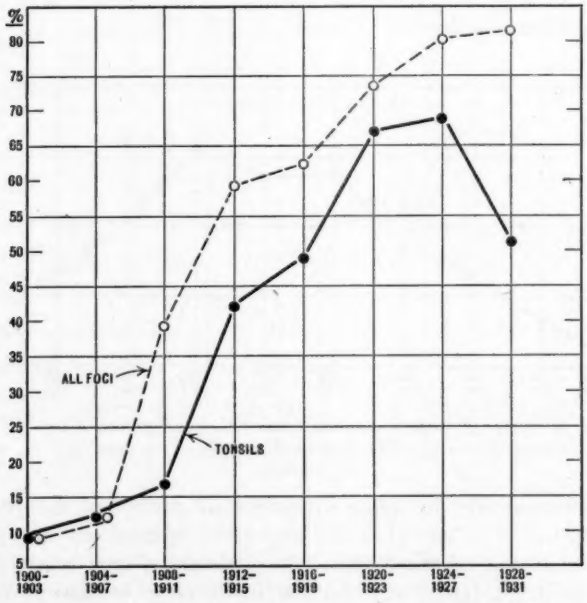
GRAPH 5.—Incidence of acute rheumatic fever with temperature of 104° F. or higher (St. Luke's Hospital).

It is unnecessary to make an extended survey of the literature here. Suffice it to say that the expressed opinion on the question of the incidence of rheumatic fever is varied and contradictory. This is at least partly due to the incomplete statistical analyses which have served as their basis.

In the present series the records of 787 cases of acute rheumatic fever at St. Luke's Hospital and of 365 cases at the New York Post-Graduate Hospital have been studied. Since 1898 there have been

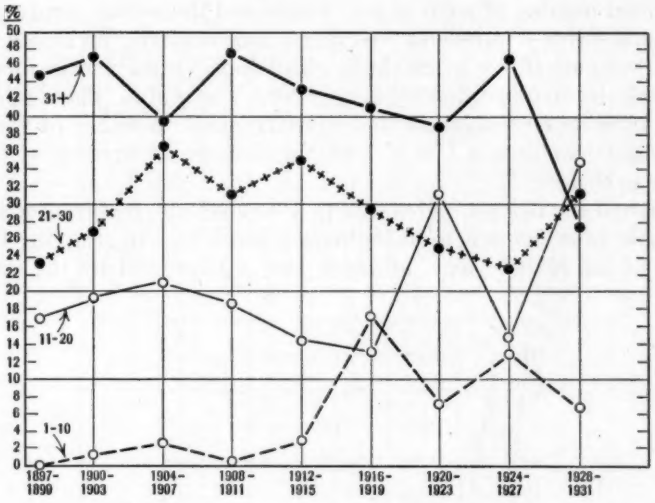


GRAPH 6.—Incidence of cardiac disease in acute rheumatic fever (St. Luke's Hospital).



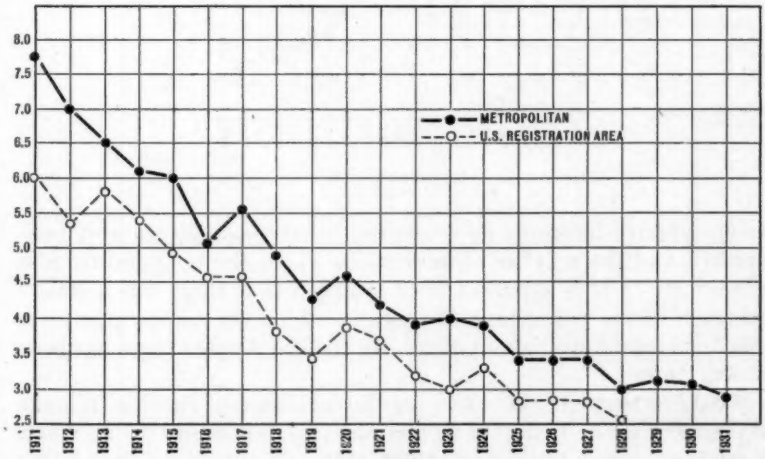
GRAPH 7.—Incidence of focal infection (St. Luke's Hospital).

wide fluctuations in the number of admissions of patients with rheumatic fever to the two hospitals under investigation. In spite



GRAPH 8.—Incidence of rheumatic fever according to age (St. Luke's Hospital).

of the variable incidence there appears to have been a steady decline both in the absolute number of admissions of rheumatic fever

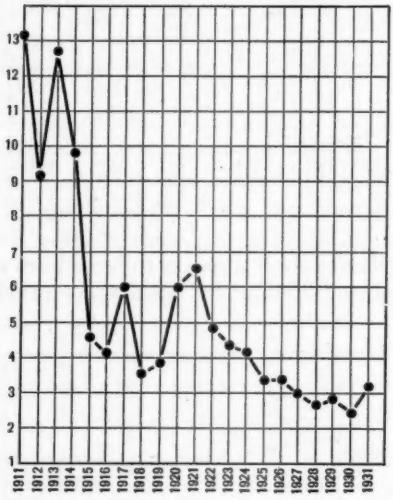


GRAPH 9.—Death rates per 100,000 from acute rheumatic fever.

cases and in the relative number, *i. e.*, as compared with other diseases. This condition lasted until 1919, since when there has

been a slow increase in both absolute and relative number of admissions. Graph 2 shows the incidence of acute rheumatic fever at St. Luke's Hospital from 1897 to 1931. On this graph is also plotted the annual number of medical admissions and the actual number of rheumatic fever admissions. Graph 3 indicates the incidence of acute rheumatic fever at St. Luke's and New York Post-Graduate Hospitals, located in different parts of New York City. The similarity of these curves suggests that a study made in either of these hospitals might give a fair idea of the average occurrence of the disease in this city.

Although the disease still occurs in a severe form, recurrences are less liable to occur now than formerly (Graph 4). In studying the charts of the earlier years, however, one is impressed by the rela-



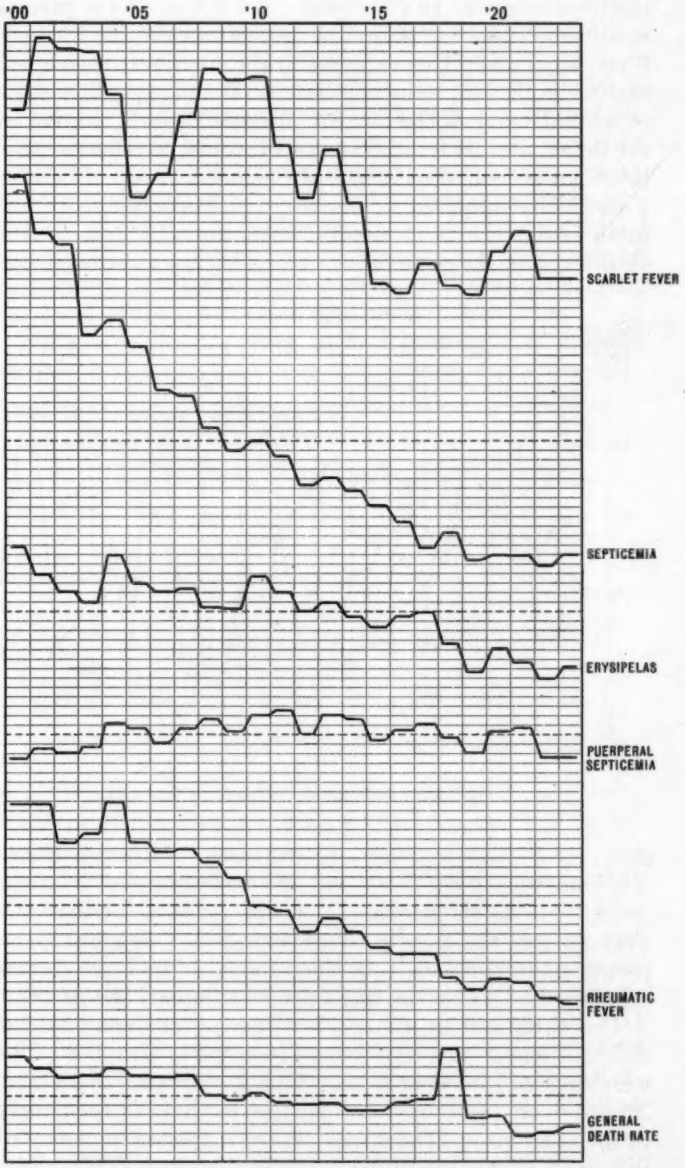
GRAPH 10.—Death rate from scarlet fever.

tively greater intensity as evidenced by the complication of pericarditis and the number of patients in whom the temperature rose above 104°. It is apparent from Graph 5 that there was a steady increase in the percentage of cases in which the temperature was 104° or greater until about 1923. In the last 6 years there has been a definite fall.

Graph 6 presents the curve for the incidence of carditis in acute rheumatic fever. It fluctuates considerably, but shows on the whole a tendency to rise until about 1919. After that there is a drop in the general slope of the curve. The graph for the cases from the New York Post-Graduate Hospital is again similar to that for St. Luke's, so we have not reproduced it here.

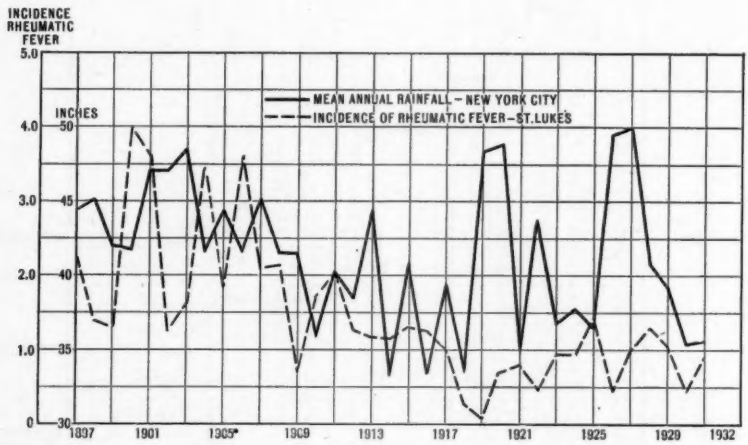
It is obviously impossible to take into account all the conditions

affecting the incidence of the disease, but four possible points suggest themselves as being of primary significance.



GRAPH 11.—A comparison of the death rates in the U. S. Registration Area from scarlet fever, septicemia, erysipelas, puerperal septicemia and rheumatic fever for the period 1900–1923.

First. *The Problem of Removal of Foci.* There has been an increasing tendency in recent years to look for and remove foci of infection. Graph 7 shows the great increase of foci found and removed at St. Luke's Hospital since 1900. If the presence of foci is an important factor in the general susceptibility to rheumatic fever, then one might expect a graph for the frequency of this disease to be the reverse of that for foci found and removed, with a lag of several years in the former. In other words, a great increase in the detection and treatment of foci would be reflected several years later in a decreased incidence of rheumatic fever. But when Graphs 2 and 7 are compared we find a gradual decrease, with fluctuations, in the incidence of rheumatic fever until 1919, with a coincident steady rise in the removal of foci. This rise continues, but the inci-



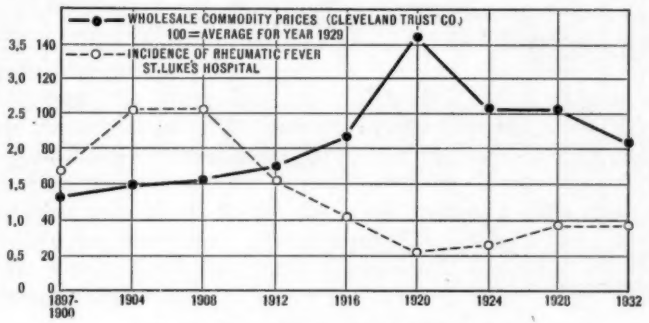
Graph 12.—Relation of moisture to rheumatic fever.

dence of rheumatic fever also increases. Although there has been a recent drop in the frequency of tonsillectomies, it cannot be held responsible for the increase in rheumatic fever, because this increase began before the drop in tonsillectomies. Our graphs, then, do not permit us to conclude that the removal of foci of infection has any significant effect on the incidence of rheumatic fever.

The variations in the number of cases of rheumatic fever in the different age groups have been presented in Graph 8. The patients were divided into four groups: 1 to 10 years, 11 to 20, 21 to 30, and 31 and over. Inspection of the curves leads to the conclusion that in the older groups the disease shows a greater tendency to decrease in recent years than in the younger groups. This might possibly indicate that the older people are now deriving some benefit from

removal of foci at earlier ages, except that we have seen from Graph 7 that the relation of the presence of foci to rheumatic fever is very doubtful.

SECOND. *The Possible Cyclical Character of Rheumatic Fever.* It has been said that rheumatic fever follows a cycle similar to that found in many acute infectious diseases. The rapid fall in the mortality of acute rheumatic fever from 1911 to the present is seen in Graph 9. These curves were supplied by Mr. Van Buren, statistician of the Metropolitan Life Insurance Company. Not only is there a rapid fall in the mortality, but the curve may be considered to be made up of four fairly similar cycles of 3 to 5 years each, characterized by a sharp rise and subsequent gradual and more prolonged fall. Graph 10 shows a fairly similar mortality curve for scarlet fever. Whether the similarity of the curves indicates a changing degree of virulence of the infection or whether it indicates improving hygienic conditions which are reflected in decreasing susceptibility



GRAPH 13.—American business activity.

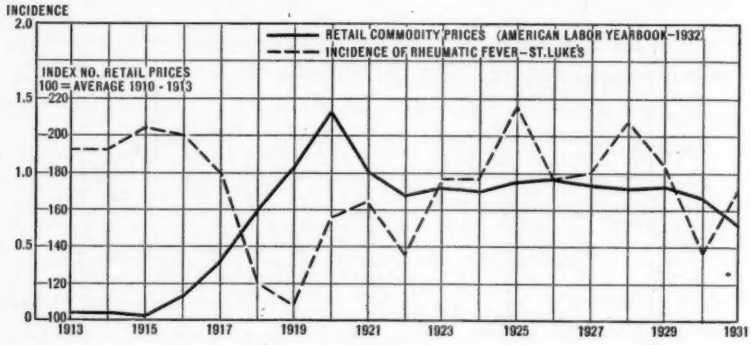
to infection is difficult to say with the data at hand. It is equally probable that the changes in mortality of the two diseases do not have a similar cause at all.

Graph 11 is reproduced from a paper published by Atwater[5] in 1927 on the epidemiology of acute rheumatic fever and related diseases in the United States based on mortality statistics and covering the period 1900 to 1923. He concluded that the history of the disease in the United States during the past half century showed a striking decline in the number of deaths and probably in the number of cases as well. The graph shows the parallelism between the proportion of deaths due to rheumatic fever and to streptococcal diseases, and the apparent cyclic character of these diseases.

THIRD. *The Question of Rainfall.* The disease is more prevalent in periods of greater rainfall. It is well known that rheumatic

fever is a disease of cold, damp countries, occurring mostly along the coast, river bottoms and canals. This fact suggests that years of increased rainfall might be marked by an increase in the incidence of acute rheumatic fever. This relationship is shown in Graph 12. The average annual rainfall was taken from the figures of the weather bureau in New York City.[6]

If it is true that rheumatic fever is more liable to occur in wet weather, then a rise in the rainfall curve ought to be accompanied by the curve for the incidence of rheumatic fever within the following year. When we examined the rheumatic fever curve after the seven rainiest years, we found a rise in 6 instances, whereas after the 7 driest year there was a subsequent drop in 4 instances, a rise in 2 and no change in 1. It seems justifiable to draw the conclusion that wet weather is one of the factors increasing the prevalence of rheumatic fever. In contradiction to this conclusion, Newsholme[7]



GRAPH 14.—American business activity.

has reported that in England there is an increase in rheumatic fever in dry years, and he attributed this to the increase in the amount of dust and the consequent greater ease of spreading infections.

FOURTH. *The Question of Economic Status.* Acute rheumatic fever seems to be a disease of the poorer classes and would therefore be more liable to be widespread at times when more people are deprived of adequate food, clothing, fresh air and medical attention. It is almost impossible to choose a satisfactory index for the general cross-sectional economic welfare of the inhabitants of New York City. Since there are no reliable statistics on the number of unemployed, it would be very inaccurate to use average weekly earnings. The income tax report is likewise unsatisfactory because it gives no idea of the economic fluctuations of the large group who do not pay a tax and with which we are mainly concerned. In

this study we have first plotted the curves for the wholesale commodity prices (Graph 13), which give a fairly good index of business activity. Graph 14 shows the fluctuations in the average retail prices of 30 basic commodities, and from this some idea of the variation in the cost of living can be gained. In both these graphs the important points to be observed are the rise in economic activity until 1920 which was followed by a sharp fall and the next period of stability which was broken by the crash of 1929. If we attempt to correlate with this the curve for the incidence of rheumatic fever we find that a fairly good reciprocal relationship manifests itself in Graph 13. In the more detailed graph (Graph 14), the correlation is not so uniform. It is true that the incidence drops during the first period of "prosperity," but it had already begun to rise before the 1920 depression was well under way. Inspection of the graph reveals other definite discrepancies and, on the whole, hardly seems to lead to the conclusion that fluctuations in economic welfare and the morbidity of rheumatic fever go hand in hand. The statistics for this year, however, will be interesting in this connection because of the sharp rise in unemployment and distress in the lower middle class group.

Summary. 1. There has been a decline in the incidence of acute rheumatic fever at both St. Luke's Hospital, New York and the New York Post-Graduate Hospital from 1897 to 1919 and a rise since that time.

2. Four possible factors have been discussed with reference to this changing incidence: (*a*) Removal of foci of infection; (*b*) Cycles in the virulence of infectious diseases; (*c*) Rainfall; (*d*) General economic conditions.

The author wishes to express his appreciation to Dr. Lewis F. Frissell who suggested this survey and to Dr. Walter Lough for his suggestions and help.

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GASTRITIS IN ITS RELATION TO OTHER DISEASES.*

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Gastritis, which may be defined broadly as a diffuse degenerative or inflammatory disease of the mucosa of the stomach, was looked upon during the latter part of the past century as the common cause of indigestion and responsible for many other ills of the body. With the discovery that the microscopic mucosal changes described by the pathologists of that time were due to postmortem autolysis and with the coincident popularization of the stomach tube, attention gradually shifted to the secretory disturbances of the stomach. Even the advanced types of chronic gastritis, recognizable by gross atrophic and hypertrophic changes, lost their interest for the pathologist and clinician, and for a time no attempt at correlation of the anatomic and secretory alterations was made. Although Faber and Lange,[1] in 1908, making use of a technique introduced 18 years before by Hayem for prompt fixation of the gastric wall at death, described minute inflammatory changes of the stomach mucosa that were associated with achylia, their work attracted relatively little immediate attention. This was probably due, in part, to the fact that at the same time gastric ulcer, gall bladder disease, and appendicitis were being recognized as frequent causes of indigestion. Even now, in spite of the great interest in the gastric secretory disturbance demonstrated by Castle[2] as responsible for Addisonian anemia, some of the textbooks on pathology entirely neglect the subject of gastritis, and at most autopsies only a brief note on the gross appearance of the stomach is made.

Faber,[3] however, has continued to emphasize the significance of gastric inflammatory changes in relation to disturbances of stomach secretion. He considers that a mild or localized gastritis may exist with the acid secretion intact or even increased, while any diffuse form, especially that with advanced glandular atrophy, leads to a marked reduction or absence of such secretion. Orator[4] and Konjetzny,[5] basing their work chiefly on the study of resected specimens, have arrived at much the same conclusions. Hurst,[6] who like Conner[7] and Wilkinson[8] believes in an hereditary or constitutional factor in the development of achlorhydria in some instances, insists that it is usually explainable on the basis of a gastritis. He has demonstrated that often a recovery of acid secretion may be

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obtained by hydrogen peroxid lavage, even occasionally when the histamin test has been negative, and considers this as strong evidence in favor of the gastritis being primary. He has observed cases of pernicious anemia with achlorhydria in which the onset of symptoms dated from an acute gastritis. Additional support for the contention that gastritis leads to a loss of acid secretion is found in the rising incidence of achlorhydria with age. A lack of mucus in the gastric contents, which usually is present with achlorhydria, does not eliminate gastritis as the causative factor, because in the advanced atrophic stage no secretion whatever may be possible. Finally, from the clinical viewpoint, I have observed many cases of achlorhydria in which roentgenologic study showed the typical signs of hypertrophic gastritis.

From the point of view of the pathology involved it may be said that while those especially qualified to speak, such as Faber, Konjetzny, Orator, and Hillenbrand,[9] are by no means in entire agreement as to the anatomic criteria which separate the borderline cases into normal and abnormal groups for certain age periods, it does seem clear from their investigations that a so-called chronic gastritis consisting of an extensive glandular atrophy, often with gland change to the type of the small intestine, an increase in follicular centers, round cell infiltration between the glands, and eventually destruction of the glandular structures with overgrowth of fibrous tissue frequently occurs, particularly in persons past middle life. These changes may be present in either of the gross types of chronic gastritis, usually referred to as hypertrophic and atrophic.

My interest, aroused in this subject some years ago, has been intensified by Castle's researches and Hurst's clinical observations. For 2 years W. O. Abbott, of our clinic, has been injecting with formalin solution the stomachs of patients dying in our wards and securing specimens from such of them as came to autopsy; these, with resected specimens obtained at the operating table, he has subjected to careful microscopic study. His work will be reported in detail separately, but I may say here that it tends to support the contention that chronic gastritis and achlorhydria are usually associated.

Although it is still impossible to state with certainty which is primary, the gastritis or the secretory dysfunction, the mere fact of their common association justifies consideration of chronic gastritis in its relation to some of the other diseases in which achlorhydria is usually found. These are Addisonian anemia, other anemias of the chlorotic or microcytic type, subacute combined degeneration of the spinal cord, carcinoma of the stomach; sometimes diarrheal diseases, such as sprue; less frequently diseases of the gall bladder, arthritis, etc. The achlorhydria itself has not been proved to be of etiologic significance in any of these diseases, but it is reasonable to assume that the lack of hydrochloric acid

may be only one evidence of an altered mucosa, and that other associated disturbances, such as a lack of the intrinsic factor of Castle in Addisonian anemia, may be on a similar organic basis.

Relationship to Other Diseases. Since, then, a so-called chronic gastritis, consisting of more or less diffuse degenerative and inflammatory changes, and usually characterized clinically by a hypochlorhydria or an achlorhydria, is recognized, we are prepared to consider in relation to this disease of the stomach some of the other diseases with which achlorhydria is commonly associated. I shall refer at this time to only two of them: gastric carcinoma and Addisonian anemia.

(*A*) *Gastric Carcinoma.* With the exception of the cases that are secondary to ulcer (probably not more than 10 per cent) and those that are secondary to benign polyp (probably not more than 5 per cent) we have had in the past no very clear conception regarding the predisposing factors in the production of gastric cancer. For the majority group, however, including those on a polyp basis, and in definite contrast with those on an ulcer basis, two clinical facts stand out prominently: (1) that they usually present no pre-cancer symptoms, and (2) that an achlorhydria is commonly present. The absence of a previous gastric history has been responsible for the idea, still in vogue, that this type of carcinoma springs *de novo* from a normal gastric wall, but the associated achlorhydria is not consistent with such a theory. This becomes manifest when attention is directed to the following considerations:

1. The patients who are believed to have developed cancer on a stomach ulcer basis show no progressive decrease in gastric acidity, this indicating that the achlorhydria is not a secondary development. We have usually found free acid in our cases that gave a long ulcer history, no matter what the stage of the malignant process. Hurst had 3 such cases followed for a considerable period of time, and found no decrease in the acidity; he has not seen a case in which acid was once present and later in the disease disappeared. In 12 of 14 ulcer-cancer cases reported by Orator,[4] and in 9 cases reported by Stewart[10] in which acid was at one time present, it persisted to the end. Polland and Bloomfield[11] report 2 ulcer cases in which the acidity was higher after the secondary development of cancer.

2. On the other hand, the achlorhydria usually found in the majority group, those with a short history and nothing to suggest a preceding ulcer, has been demonstrated in a few cases before the development of cancer. Hurst[6] has cited a case that had achlorhydria 2 years before the development of recognizable cancer; Alexander,[12] 1 with achlorhydria 26 months before; Veale,[13] 1, 3 years before; Porges,[14] several, for years before. The scarcity of such reports is not surprising since gastric analyses are rarely done on patients without gastric symptoms.

Furthermore, it is now appreciated that carcinoma of the stomach not infrequently develops in patients the subject of Addisonian anemia, such patients almost always having had an achlorhydria for a long time. We have had at least 3 instances of gastric cancer in pernicious anemia cases, and Hurst[6] has reported 5 such cases. In 1 of his cases the carcinoma developed 9 years after onset of the anemia and 4 years after its cure by the use of liver. In this case a partial gastrectomy was done and a section from the unaffected fundal portion of the stomach was removed for study: this showed atrophic glandular changes. Hurst has also referred to the relatively high incidence of carcinoma of the stomach and of pernicious anemia in different members of the same family. The age and sex incidence for the two diseases is also much the same.

3. The prognosis after operation in the gastric cancer cases with free hydrochloric acid is no better, in fact not so good, as in those with achlorhydria. This is our own impression, is confirmed by Hurst, and is the experience of other clinicians. It would be the reverse if the achlorhydria were a secondary development and so indicative of more advanced malignant change.

Thus, it seems clear that the achlorhydria present in the majority of cancer of the stomach cases cannot be attributed to the cancer itself. Since, however, we have presented evidence to indicate that such achlorhydria is usually associated with chronic gastritis and that such gastritis ordinarily gives rise to no symptoms, an antecedent gastritis may be considered as an explanation for the lack of hydrochloric acid.

In this connection our reference to the fundus specimen secured by Hurst in a case of pyloric cancer, and which showed atrophic changes, assumes significance. Furthermore, Konjetzny and Salzman[5] have showed histologic transitions from chronic gastritis to cancer. According to Bloomfield and Polland,[15] Lebert, in 1878, found in 41 of 56 cancer cases an extensive gastritis, even at a distance from the growth, and was the first to point out the relationship. Orator,[4] by more modern methods, has demonstrated to his satisfaction such a lesion in 19 of 20 so-called "primary" carcinomatous cases, whereas in ulcer-cancer such gastritis as he found was localized about the malignant lesion only, usually in the pyloric end of the stomach, and did not involve the fundus.

Abbott, of our clinic, has had in his series of stomach specimens 11 from cases of gastric cancer: in 4 an achlorhydria had been demonstrated by fractional or histamin test; in 3, the free acid was within normal limits, and in 4 no gastric analysis had been made. Of the 4 with achlorhydria all gave a short history, averaging 8 months; while the duration of digestive symptoms in the 3 cases with acid was respectively 13 months, 5 years, and 42 years. In only 2 of the cases, both with achlorhydria, did he have the entire stomach, and in both of these an extensive atrophic gastritis

was present; the others, including those with free acid, also showed atrophic or hypertrophic gastritis, but only the parts of the stomach near the malignant lesion were available for study.

Eliason and the author[16] found evidence of gastritis, usually hypertrophic, in our 8 cases of polyp-cancer, though in some instances the malignancy was just beginning: in all of them an achlorhydria was present.

Thus certain data are available to indicate that a gastritis, responsible for achlorhydria, has preceded some cases of gastric cancer, and probably such a lesion, unrecognized, has been present in many more.

(*B*) *Addisonian Anemia.* Equally interesting is the consideration of primary pernicious or Addisonian anemia in connection with gastritis. Even before the demonstration by Cahn and von Mering[17] in 1886, that achlorhydria was usually associated with this type of anemia, atrophic changes in the gastric mucosa were demonstrated by Fenwick[18] in this disease. He, together, with Quincke, Nothnagel and Ewald, who also called attention to the relationship, regarded the gastritis as primary. The earlier references to the stomach alterations must now be disregarded, however, due to doubt concerning postmortem effects; but, in 1900, Faber and Bloch,[19] using an acceptable technique, described extensive changes in the gastric mucosa of 2 patients dying of this disease: a diffuse inflammation leading to destruction and atrophy of the glands, most severe in the cardia and decreasing toward the pylorus. They were inclined to believe, at that time, that the gastric affection and the blood changes were in common due to a toxic or infectious cause.

Herzberg,[20] in 1911, after a very careful study of the stomachs of primary anemia cases, in many of which she found a severe atrophy of the mucosa, inferred that it was improbable that the gastritis was primary. She admitted, however, that the gastric changes often were found in the early stage of the anemia, and found no such changes in the secondary anemias. She also believed that the gastric and blood changes were due to the same cause.

It is probable, unless it becomes possible to produce pernicious anemia experimentally, that a determination as to which, the anemia or the gastritis, is primary can never be made on purely pathologic-anatomic grounds. Sections from the stomachs of persons who later develop pernicious anemia are not likely to become available for microscopic study. On a clinical basis, however, we now have reason to believe that the gastritis appears first.

This conclusion is based, in the first place, on the observations of many workers that achlorhydria, which certainly is the outstanding clinical sign of gastritis, frequently precedes the development of pernicious anemia. Faber and Gram,[21] Sturtevant,[22] Riley,[23] and Conner[7] had cases that showed an achlorhydria from 4 to

25 years before the development of pernicious anemia. Moschcowitz[24] especially has claimed that because it exists throughout the disease, does not disappear during remissions, and has been found so often to precede the onset of the anemia, the achlorhydria must be looked upon as primary.

Secondly, pernicious anemia not infrequently occurs in persons in whom the diagnosis of chronic gastritis has previously been made. Hurst[6] refers to its development in 4 patients who were chronic alcoholics, and in 1 of these he observed a return of acid after treatment of the gastritis. In 3 other cases of pernicious anemia, believed to have developed on the basis of a gastritis, he got a return of acid after treatment, this suggesting that the gastritis was not of the completely atrophic type. Torrey[25] tells me of 3 of his cases of alcoholic gastritis that late in the disease presented the picture of this type of anemia together with marked cord changes. I have had 1 such case on an alcoholic basis in which a small amount of free acid was demonstrable: the anemia responded readily to liver therapy.

Finally, roentgenologic study sometimes demonstrates an advanced hypertrophic type of gastritis in pernicious anemia cases. In our last 27 cases so studied, 7 showed such marked hypertrophy of the gastric rugæ that it seems impossible that it could have developed within the time that the patients had been anemic.

Similarly suggestive of the primary importance of gastric mucosal changes in Addisonian anemia, and of even more immediate interest, is the clean-cut demonstration by Castle[2] that the absence of an intrinsic factor, normally secreted by the stomach, causes the disease. Such a secretory disturbance, like the achlorhydria, can most easily be explained on the basis of an anatomic change in the gastric wall.

Conclusions. 1. Chronic gastritis, manifested clinically by a decrease or absence of hydrochloric acid and sometimes by the presence of mucus in the gastric contents, is commonly found in association with carcinoma of the stomach and Addisonian anemia.

2. Evidence is presented to indicate that such gastritis usually precedes the development of these diseases and is a factor in their origin.

3. Since the etiology of chronic gastritis, its various forms and the means of recognizing it clinically are not understood, it is obvious that if we are to prevent its development and the diseases for which it seems to be responsible, much experimental and clinical investigation is clearly indicated.

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THE REDUNDANT DUODENUM.

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Anomalies of the duodenum are not infrequently observed in the routine roentgenologic examination of the gastrointestinal tract. In recent years greater attention has been directed to this portion of the bowel, and abnormalities have been commonly noted which have hitherto escaped recognition. Anomalies of the duodenum are much more common than a survey of the literature indicates. Clinically, but little attention has been directed to these conditions up to a comparative short time; but considerable importance is now attached to them especially in regard to their etiologic relationship to the production of digestive symptoms. Recent literature abounds with individual case reports of various anomalies of the duodenum, which have been especially discovered as a result of a more thorough roentgenologic investigation. Such cases are, however, rarely recognized by any other method of examination. Most of these findings cannot be termed as definite clinical entities and the clinical signs of this group are rarely distinctive or characteristic. The diagnosis must necessarily depend upon a painstaking Roentgen study.

Too often, however, these anomalies escape the observation of the

roentgenologist and thus remain undetermined. It is probably true that with better Roentgen technique and more thorough investigations they will become more frequently recognized and their full significance brought to light.

The duodenum, about 10 inches in length, has a definite configuration in the shape of an incomplete circle or C-shaped, which under abnormal conditions may take on bizarre forms, such as the U-shaped, V-shaped and other distortions (Fig. 1).

The first part of the duodenum is the most mobile, but the remaining portions are practically fixed and bound down to adjacent viscera and to the peritoneum. The first portion of the duodenum, the most movable, is more or less fixed by the hepatoduodenal ligament, the free margin of the lesser omentum. A fold of the hepatoduodenal ligament extends down from the posterior surface of the gall bladder to the descending portion of the duodenum—the hepatocolic ligament. This ligament, however, is not constantly present. From the above description it is evident that the hepatoduodenal and hepatocolic ligaments play an important rôle in the fixation of the superior segment of the duodenum. These ligaments are responsible for the maintainance of the looping of the redundant duodenum.

In this study I desire especially to call attention to a redundant condition of the superior portion of the duodenum. This is an interesting anomaly which frequently passes unrecognized. During our routine roentgenologic study of the gastrointestinal tract I have encountered in a number of instances an elongation or lengthening of the superior portion of the duodenum. In all, a ptosis of this segment resulting in an abnormal loop was observed, which produced a puddling and retardation of the contrast meal like a water trap in which the passage of the opaque meal is somewhat blocked. The superior angle appears definitely fixed and displaced distally. In addition, the superior segment of the duodenum is fixed at its proximal portion, viz., at the junction of the first part or cap with the second part of the duodenum. The unusual lengthening of the superior segment results in a sagging, ptosis and looping, producing the characteristic picture of the redundant duodenum. The two fixed points in the superior portion are well illustrated in Figs. 1, 2 and 3.

Roentgenologically this elongated segment of the superior duodenum varies in length from 5 to 10 cm. Several types have been observed, such as the U-shaped, V-shaped, double looping and the serpentine forms. Occasionally only a sagging of the elongated segment is noted. These types are illustrated in Fig. 1.

Under normal conditions the Roentgen examination of the duodenum presents the first portion or bulb surmounted directly upon the pyloric outlet, which is directed upward, slightly to the right and somewhat posteriorly. This is commonly known as the superior

portion and is usually not more than 5 cm. in length. At the apex of the bulb or duodenal cap, the second portion is observed to form an angle with the first part and then descends downward to the right and posteriorly. No transverse elongation of this section of the duodenum is observed normally. The angulation of the superior portion is easily recognized and is more or less fixed by the hepatoduodenal ligament. From this angulation the descending portion seems to take a sudden drop. However, where the redundant duodenum is noted, this picture is quite altered into a marked elongation or lengthening of the superior segment. The duodenal cap is not

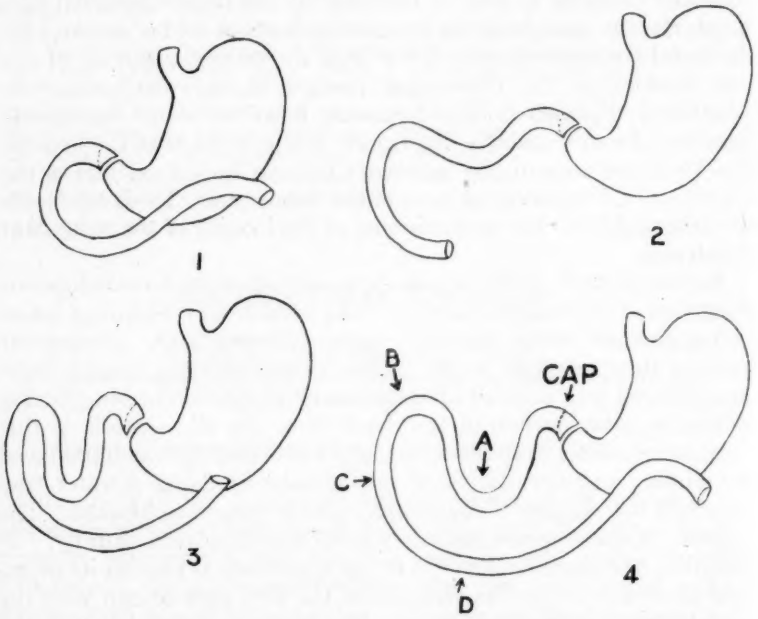

FIG. 1.—Diagrammatic drawing, illustrating the redundant duodenum. 1, Normal duodenum; 2, sagging elongated superior segment; 3, V-shaped, water trap effect of superior duodenum; 4, U-shaped, *A*, *B*, *C*, *D*, described in Fig. 2.

affected and seems to be normal in position and in size. In some instances at first glance the extra loop appears as an integral part of the cap which produces the appearance of an enlarged cap or diverticulum. This is due to the coalescing of the extra loop with the cap shadow, but upon manipulation no connection with it can be demonstrated.

Redundancy of the Superior Duodenum and its Clinical Significance. This form of anomaly has been variously described as ptosis, festooning or extra looping, terms which cannot be considered satisfactory. It is apparent that, since the duodenum is of greater

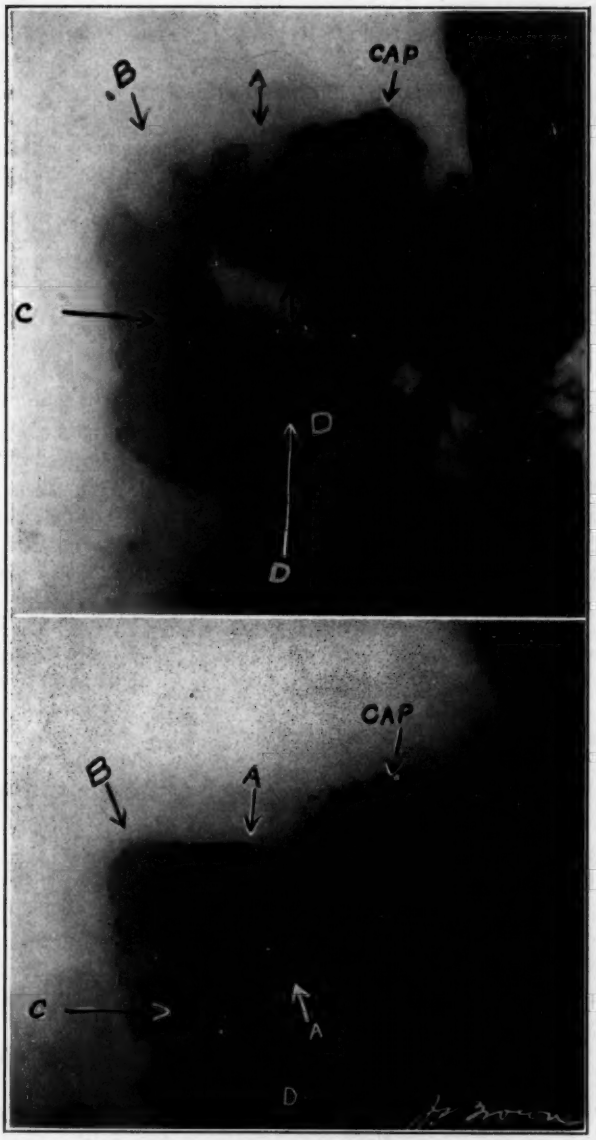

FIG. 2

FIG. 3

FIG. 2.—The lengthened duodenum with looping at *A*. This also illustrates the two fixed points. 1, at cap, representing the hepatoduodenal fixation, and 2, at *B*, the hepatocolic fixation; *C*, descending duodenum; *D*, transverse portion.

FIG. 3.—The unusual length of the superior duodenum with the extra loop, or water trap at *A* is shown.

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length than normal, the term redundant duodenum should be adopted as being more accurate as well as descriptive, and fitting more definitely with such redundant affections of a similar type as, for example, the redundant colon.

The material selected for this study comprises a group of 10 cases, all of which present a definite elongation of the superior portion of the duodenum with sagging and looping of the segment. Increasing interest is now being attached to this anomaly due to its effect upon the motility of the duodenum and the production of a condition which may have considerable significance in the formation of ulcerations in this area. As a result of the diminished motility with consequent stasis as well as retardation and lagging as is revealed by the contrast meal, this factor may easily play an important rôle in the production of such disturbances. An early recognition of this anomaly is essential in order to establish effective treatment, which should be instituted early so as to eliminate the possibility of secondary complications which may readily occur. In the diagnosis, other factors simulating this anomaly must be borne in mind, such as adhesions of the duodenum secondary to a gall bladder infection.

The redundant duodenum must be regarded as a definite easily recognized roentgenologic entity. These cases rarely present any signs of gall bladder infection. On the other hand, in nearly every instance in this series a typical or atypical picture of an ulcerated duodenum was found. In some instances, even when the roentgenologic appearance of ulceration is absent, the clinical picture frequently is that of ulcer. The association of ulceration with this anomaly is very significant. In those instances in which ulceration was not found, Roentgen evidence of duodenitis was observed.

In this series of cases the Roentgen examination presented evidences of ulceration in 5 instances; duodenal in 3, pyloric in 1 and gastric in 1. Duodenitis was present in the remaining 5 cases. Duodenal stasis, lagging and retardation was observed in every instance.

It seemed of importance to determine whether the relative position of the stomach and colon had any definite relationship to that of the redundant duodenum. In 5 instances the position of the stomach and colon was observed to be normal; in 1 a slight ptosis was noted; in 1 a moderate ptosis and in but 3 was there marked ptosis of the stomach and colon. It may, therefore, be concluded, at least from these findings, that the position of the stomach and colon bears no special relationship to the redundancy of the duodenum.

The gastric acidity was normal in 3 cases; a hyperacidity occurred in 6 and an achylia in 1.

Age seems to be an unimportant factor. In this series the ages ranged between 26 and 57 years.

Sex. There were 8 males and but 2 females in our cases, indicating that the redundant duodenum is probably more frequent in the male sex.

The diagnosis is not, as a rule, possible from the history and physical findings and must be based largely upon a Roentgen investigation. Though the condition is best recognized under the fluoroscope, this anomaly may also be recorded on the films, when placed in the proper position. The fluoroscopic examination is usually best made with the patient in the upright posture, viewed anteroposteriorly, obliquely and laterally. Examinations should also be made routinely in the prone position. In the fluoroscopic examination one can manipulate the entire duodenum and especially bring into view the redundant segment, which may otherwise not be visible. Most frequently one observes a puddling in a loop hanging from the midsuperior portion of the duodenum, between the cap and the descending sections. As has already been stated this has the appearance of a water trap, which definitely retards the outflow of the contrast meal and which at once gives a clue as to the possibility of the presence of this abnormality. On manipulation this puddling entirely disappears, only to return on the next spurt of the opaque meal through the duodenum.

Roentgenologically a double fixation of the superior duodenum is presented in this group of cases, which is not due to acquired adhesions, but represents most likely a congenital anomaly. The fixation is due to the presence of peritoneal bands, represented by the hepatoduodenal and the hepatocolic ligaments. The presence of a redundant superior duodenum is best explained upon the basis of a congenital formation, in which the duodenum is lengthened, so that it cannot fit into the space alloted to it. This anomaly therefore seems to be dependent upon the unusual length and abnormal fixation of the superior portion of the duodenum.

As a result of this anomaly, the duodenum frequently becomes irritable and produces the Roentgen signs of a duodenitis. A prolonged stasis was not observed in our cases. The caliber of the duodenum was not enlarged nor was there any evidence of chronic obstruction. No abnormal or exaggerated retroperistalsis was observed in this group.

Conclusions. 1. Ten examples of redundant duodenum have been studied and their significance evaluated.

2. The redundant segment occurs most frequently in the superior portion.

3. The redundant duodenum is not an infrequent condition, being more common than is ordinarily recognized.

4. The clinical significance of the redundant duodenum has as yet not been fully established.

5. The coexistence of ulceration with the redundant duodenum is not unusual.

6. The Roentgenologic method of examination offers the best possible means of establishing the diagnosis.

THE CORRELATION OF OTHER DIAGNOSTIC PROCEDURES WITH CHOLECYSTOGRAPHY IN 250 CASES OF SUSPECTED GALL BLADDER DISEASE.

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The following analysis of data on 250 recent ambulant and hospitalized patients who, on cholecystographic study, gave evidence of gall bladder disease has been made with two purposes in mind: to test further the reliability of that diagnostic procedure and to determine to what extent other common factors in diagnosis could be correlated with it. No selection of cases has been made except to omit such suspected ones as had negative cholecystograms. This both eliminates the possibility of detecting cholecystographic errors in which disease is present, but is not demonstrable roentgenologically, and fails to give convincing proof of the presence of disease in the cases not operated upon. With these limitations, however, it seems a reasonable approach to the matter of evaluating the significance of the roentgenologic diagnosis of gall bladder disease. At the same time it affords an opportunity to place a relative value on all the diagnostic procedures commonly employed.

The two propositions just outlined were checked by operation in 74 instances (30 per cent). In 176 cases each diagnostic procedure was evaluated in the light of the conclusion reached from the assembled clinical data of the case.

The clinical history, physical examination and cholecystogram now comprise in most clinics an irreducible minimum in the diagnostic study of gall bladder disease not associated with common duct obstruction. In addition to these procedures, which were carried out on all patients of the present series, the following tests were performed in sufficient number to be of statistical value: fractional gastric analysis after a gruel test meal in 184 patients, after histamin in 8, gastrointestinal roentgenography in 117, van den Bergh test in 108 and duodenal drainage by the technique of Jones[1] in 95. An attempt is made to determine the significance in diagnosis of the incidence of other disease along with cholecystitis. Follow-up data on the surgically treated cases are included for the sake of completeness.

The position of the Graham-Cole test as a diagnostic aid is being constantly strengthened by perfection of the technique and by the

publication of comparative figures such as these. In a former paper[2] the limitations of both peroral and intravenous cholecystography as practised in this hospital were summarized and the conclusion reached that in doubtful cases the intravenous method should be used as a check on the routine peroral test.

Recent reports on the effectiveness of special diagnostic tests include cholecystography, but fail to correlate with it all the other commonly used procedures. Bockus[3] expresses the position of those who depend upon duodenal drainage rather than cholecystography for the diagnosis of gall stones. Kirklin,[4] with a wide experience in cholecystography and a progressive attitude toward it, represents those whose reliance is placed very largely in that procedure. Dwyer and Dowling[5] present diagnostic data in regard to history, cholecystography and gastric analysis, in a report dealing particularly with the effects of cholecystectomy. Hoffman[6] studied 155 surgically treated cases to determine the degree of accuracy of certain diagnostic procedures, with emphasis, however, on the clinical data. Fleming,[7] in an appraisal of his experience in 233 proved cases, analyzed the diagnostic reliability of the Graham-Cole test alone.

Clinical History. The emphasis to be placed in this review upon cholecystography and other laboratory tests is by no means meant to detract from the value of a well-taken history. The history will be considered first because it emerges, upon analysis of these cases, the most effective single diagnostic item in 126, or half of the series. It remains the chief support in most cases for the clinician's judgment, as Hoffman[6] has recently emphasized. The consistency with which the major symptoms of intermittent right upper abdominal pain and persistent "gaseous indigestion" occur is noteworthy: One or both were present in almost every case. Other items of the history, less frequently found, will be recapitulated because their value was proved in these cases: Familial history of gall tract disease, preceding pregnancies in the patient, adiposity, distress after fatty or "rich" foods, sudden onset of pain, night attacks, nausea and vomiting, necessity for hypodermics and residual local soreness.

In general, we have not attempted to distinguish between gall stones and mere diseased gall bladder wall from the history and physical findings in the absence of jaundice. The contention that distress or pain after eating fatty foods is a differentiating symptom of cholecystitis with stones was not confirmed. In the 64 operatively proved cases distress after fatty food had occurred as a symptom in almost the same proportion of those patients who did not harbor gall stones as those who did, a distinct minority in each class. (Present in 14 cases with stones, absent in 34; present in 4 cases without stones, absent in 12.)

The age incidence of this group of patients is in accord with the

figures commonly accepted. About 80 per cent began to have symptoms between the ages of 20 and 50 years, and the same proportion presented themselves for treatment when they were between 30 and 60 years. Dwyer's figures[5] of 35 per cent below the age of 40 years at admission are duplicated (36 per cent).

TABLE 1.—SEX AND AGE INCIDENCE ON ADMISSION IN 250 CASES OF PROVED OR SUSPECTED GALL BLADDER DISEASE WITH POSITIVE CHOLECYSTOGRAMS.

Sex.	Number.	Per cent.
Females	169	68.0
Males	81	32.0
Decade		
10 to 19	2	0.8
20 to 29	24	9.7
30 to 39	63	25.0
40 to 49	78	31.2
50 to 59	50	20.0
60 to 69	31	12.5
70 to 79	2	0.8
	250	100.0

TABLE 2.—AGE INCIDENCE IN 235 CASES AT TIME OF ONSET OF SYMPTOMS.

Decade.	Number.	Per cent.
10 to 19	4	1.7
20 to 29	48	20.2
30 to 39	70	30.2
40 to 49	67	28.5
50 to 59	30	12.5
60 to 69	15	6.5
70 to 79	1	0.4
	235	100.0
Uncertain of time of onset	15	

The above age incidence figures offer nothing helpful in the differential diagnosis from peptic ulcer, a point which merits reiteration. The age curves both at onset and at admission can almost be superimposed upon those for 221 cases of proved duodenal ulcer reported in 1929 by Miller, Pendergrass and Andrews.[8] The age-at-onset curve likewise approaches closely that of Taylor and Miller[9] for a group of patients with gastric cancer believed to have arisen on an ulcer basis. (Charts I and II.)

The sex incidence figures, however, vary widely for the two groups. In the gall bladder series women predominated 2 to 1; in the ulcer series men outnumbered women 6 to 1. Unfortunately, no anthropometric data as worked out by George Draper are available.

Physical Examination. Tenderness in the gall bladder area was present in 70 per cent. The liver was palpated in 19 per cent, the gall bladder itself in only 8 instances (3 per cent). A definite Riedel lobe was described only 3 times in 250 examinations. Muscle resistance was infrequently mentioned, and presumably infrequently determined. There is likewise no indication on the records as to

the extent to which the tests for intercostal neuralgia (Carnett) were applied. Nine per cent of the group showed clinical jaundice at the admission examination.

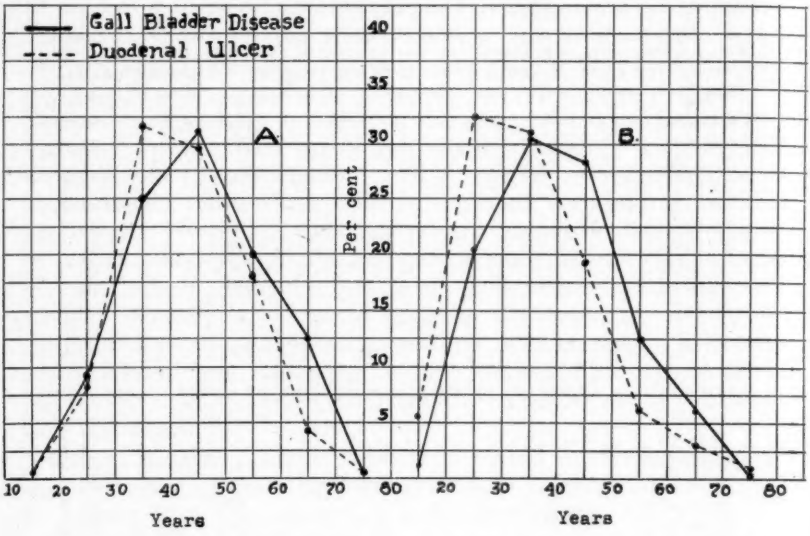

CHART I.—*A*, age incidence at time of admission to hospital of 250 gall bladder and 221 duodenal ulcer cases. *B*, age at onset of symptoms in 235 gall bladder and 221 duodenal ulcer cases.

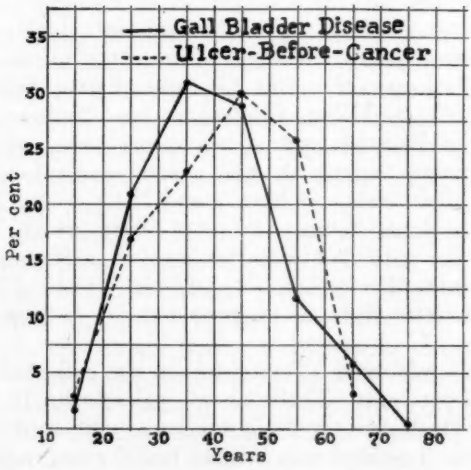

CHART II.—Age at onset of symptoms in 235 gall bladder and 31 gastric ulcer-before-cancer cases.

In summary, the records reveal a tendency to slight the secondary physical signs in these patients, and partly as a result of this the examination outvalued the history and cholecystogram as a factor in diagnosis only 9 times.

TABLE 3.—SYMPTOMS AND SIGNS.

	Number.	Per cent.
Upper abdominal pain	214	86.0
Indigestion	177	71.0
Jaundice (history)	50	20.0
Tenderness in gall bladder area	171	69.0
Liver palpable	48	19.0
Gall bladder palpable	8	3.2
Jaundice (observed)	31	12.4

Cholecystography. The Graham-Cole test compared most favorably with the history as a trustworthy diagnostic guide. It was found, after all clinical facts were in hand, to be the most valuable diagnostic item in 115 cases (compared to 126 in which the history outvalued it). The test was performed on all patients: 248 patients took the dye by mouth; 56 intravenously, in general as a check on the peroral method.

TABLE 4.—CHOLECYSTOGRAPHY VERSUS CLINICAL HISTORY AND PHYSICAL EXAMINATION.

	Number.	Per cent.
Oral cholecystograms	248	99
Intravenous cholecystograms	56	22
History most valuable item	126	51
Cholecystogram most valuable item	115	46
Physical findings most valuable item	9	3

Here, as elsewhere, one notices an occasional overstressing of the positive cholecystogram, and tendency to slight the history and other factors in diagnosis. Kirklin[4] and others have stated that the most common source of error in cholecystography is the "normally functioning gall bladder" which nevertheless reveals calculi and inflamed walls to the surgeon. On the other hand, 10 of the 74 cases of this series subjected to operative proof demonstrate again that the roentgenogram of a "poorly functioning gall bladder" occasionally is due to other than gall bladder disease or, indeed, to no adequate cause. These 10 individuals were regarded at operation as having normal gall bladders which were left *in situ*. Their cholecystograms had been made by the peroral technique and were carefully reviewed: All showed the homogeneous opaque substance in the intestinal canal which indicates that absorption of the dye has occurred. In 8 a plausible reason for the absence of shadow lay in abnormality of organs closely associated with the biliary tract (*i. e.*, liver disease, duodenal ulcer, cancer of the pancreas and pyloric stenosis). In this connection Rivers[10] has

stressed the propinquity of duodenum and gall bladder, whereby an inflammatory condition in one organ may alter the function of the other or extend to and involve it to a varying degree. Two of the 8 cases were jaundiced at the time of cholecystography and the error may have been due to this.

In 2 instances, however, operation disclosed a grossly normal biliary system and no disease of adjacent organs. In both the appendix was involved (subsiding acute appendicitis and adherent retrocecal appendix), which may have influenced the cholecystogram in a manner obscure at present. One, therefore, cannot in justice determine the true cholecystographic error in this rather large proportion of disagreement in findings. Furthermore, pathologic examination of the mucosa and walls of these gall bladders might have disclosed disease not evident to the surgeon but sufficient to interfere with function. The above 10 cases are included in the series because, largely due to the cholecystogram, they fell into the group "suspected gall bladder disease," although the preoperative diagnosis may have been that of other abdominal disorders. They illustrate the danger of the error that lies in overmuch dependence on a single test, no matter how efficient.

TABLE 5.—OPERATIVE FINDINGS IN THE 74 OF 250 CASES WITH POSITIVE CHOLECYSTOGRAMS THAT CAME TO LAPAROTOMY.

Gall bladder disease	64
Gall bladder normal, other abdominal lesions	10
Cirrhosis of liver	2
Duodenal ulcer	2
Carcinoma of pancreas with jaundice	1
Pyloric stenosis	1
Narrow common duct, with pyloric stenosis	1
Spastic duodenum, excess motility	1
Appendicitis	2

Gastrointestinal Roentgenography. We have made roentgenologic study of the stomach and intestine with the opaque meal in 47 per cent of the present series. Although detailed studies of the relationship of the alimentary tract to the abnormal gall bladder were not made, it is significant that the duodenum was deformed by adhesions in 53 per cent of the 117 cases. Among 30 proved cases 60 per cent showed such duodenal deformity. Duodenal stasis occurred in 10 per cent, while in only 24 per cent of the total was the upper gastrointestinal tract normal roentgenologically.

The procedure is indicated in obscure cases, in our opinion. The helpful diagnostic evidence to be obtained from such study is seemingly not appreciated in many American clinics, so that Rossi of the University of Parma, in describing the valuable features of his combined cholecystographic and gastrointestinal technique,[11] can with some justice write: "Almost always, especially abroad, there has been omitted an accurate study of the gastrointestinal tract." He gives the patient an opaque, fatty paste instead of the

fatty meal, and studies serially the shape, position and functional activity of the stomach and intestine while the gall bladder is contracting. Levene and Whitaker,[12] in 1930, reported good results from the simultaneous observation of stomach, duodenum and gall bladder action. Nevertheless, possibly due to the rather exacting and time-consuming technique, the combined method has not gained wide acceptance in this country.

TABLE 6.—GASTROINTESTINAL ROENTGENOGRAPHIC FINDINGS.

	In 117 patients with positive cholecystograms.		In 30 cases of diseased gall bladder at operation.	
	Number.	Per cent.	Number.	Per cent.
Deformed duodenum (adhesions)	62	53	18	60
Normal	29	24	5	17
Upper intestinal stasis	11	10	2	7
Pylorospasm or deformed pylorus	7	6	3	10
Duodenal ulcer	6	5		
Gastric polyp	1	1	1	3
Excess motility	1	1	1	3

Duodenal Drainage. This procedure has been in use in our Gastrointestinal Section since 1927. The early results on a small group of patients were reported in 1929.[13] Throughout, the technique advocated by Jones[1] has been followed with the following results in 95 cases (31 per cent): Half of the examinations offered confirmatory evidence of cholecystic disease; the other half gave results which were not helpful, in that the findings in the centrifuged sediment were entirely negative, when other evidence pointed to disease, or when in the absence of definite crystals the examiner could not be certain that the formed elements seen denoted true biliary pathology. Approximately the same results appeared in 30 cases subsequently proved.

TABLE 7.—DUODENAL DRAINAGE IN 95 GALL BLADDER SUSPECTS.

	Number.	Per cent.
Of diagnostic value (Crystals, 33)	46	48
Doubtful value (Negative, pus cells, epithelium)	25	26
No value (Disagrees with final diagnosis or operative findings)	24	26

TABLE 8.—DUODENAL DRAINAGE IN 30 CASES OF PROVED BILIARY DISEASE.

	Number.		Per cent.
Crystals	12	(stones, 10)	41
Excess pus cells	5	gall bladder ulcerating, 2; stones, 2	16
Negative	10	no stones, 6; stones, 4	33
Doubtful	2		6
Unsatisfactory	1		3

The negative drainages in positive cases, which have formed the bulk of the unsatisfactory tests to date, have, in our present

more complete knowledge of the method, been due in large part to two factors: The impossibility, until recently, in the Section or the wards of assigning the conduct of the test to a single thoroughly trained member of the staff, and an insufficient number of diagnostic drainages in the doubtful cases. Those who have reported great success with the test[3] emphasize these points. Our results have demonstrated that to be of consistent value, every step of the technique must be presided over by an expert. Provided the conditions are fulfilled, there is no doubt that the failure to obtain brown gall bladder bile or the finding of cholesterin or calcium bilirubin crystals or large numbers of deeply bile-stained pus or columnar cells is evidence of gall bladder disease.

Gastric Acidity. Analyses of the gastric contents were made with the gruel test meal in 184 of the entire group and 53 of the proved cases. The histamin test was made 31 times, in 23 instances after the gruel meal had developed little or no free acid. Of the 23 patients, 17 showed adequate acid figures under the increased stimulus. However, because of the great variability of response to histamin, precluding any "normal" standard, and because the histamin series is quite small, it is not deemed worthwhile to include it in the tabulation. Histamin is used at present in the Section only to distinguish true from false achlorhydria.

The results of the gruel meal are likewise hard to standardize and comparison with the figures in other published reports is almost worthless because of the great variation that prevails in the type of meal used and the technique of collection. However, setting the limits of 10 to 40 (cc. $\frac{N}{10}$ HCl per 100 cc.) for normal range of free acid response in the 90-minute fractional test, with gruel, the incidence of hypochlorhydria and achlorhydria in the general and the proven groups was 38 and 31 per cent, respectively. This is a distinctly higher proportion than obtains for the patients of the Section as a whole. The patients showing excess acid secretion were in small number, 10 and 4 per cent, respectively.

TABLE 9.—GASTRIC CONTENTS (FRACTIONAL ANALYSIS, GRUEL MEAL).

	In 184 patients with positive cholecystograms.		In 53 operatively proved cases.	
	Number.	Per cent.	Number.	Per cent.
Normal	96	52	34	65
Hypochlorhydria	43	23	7	12
Achlorhydria	28	15	9	19
Hyperchlorhydria	17	10	3	4

With 2 exceptions to be mentioned, the hyperchlorhydria patients gave the histories of short duration and the patients with depressed acid as a rule the longer ones. The average duration of symptoms in the high acid group including 1 12- and 1 15-year history was 3.6 years. The average for the same hyperchlorhydria patients, with these 2 histories omitted, was 2.4 years. In comparison, the

average duration for the low acid cases was 4 years, and for the normal acid cases 3.1 years.

One is justified, probably, from these results, in saying that evidence is hereby added that hypochlorhydria and achlorhydria are more common in gall bladder disease than in normal persons and gastrointestinal patients other than those with gastritis or malignancy. Furthermore, the incidence of hyperacidity is relatively small, and the condition is found, by and large, early in the disease. The discovery of depressed or absent free hydrochloric acid may thus be of use, with an extended history of indigestion, as a link in the chain of diagnostic facts denoting gall bladder pathology.

Van den Bergh Test. In the presence of clinical jaundice the van den Bergh test, repeated every few days, is of value in determining whether any regression of the jaundice is occurring. Its chief value, however, lies in the ability of the indirect reaction, with the icterus index, to pick up latent jaundice, not detectable otherwise. In the doubtful case such indication of liver or biliary tract abnormality may clinch the diagnosis. The test was performed 1 or more times on 108 individuals. It demonstrated latent jaundice, not detectable clinically, in 22 per cent; among the proved cases in 29 per cent. The test is worthy of retention in gall bladder diagnosis, indeed of more frequent application than was made in the present series.

TABLE 10.—VAN DEN BERGH TEST.

	In 108 patients with positive cholecystograms.		In 24 operatively proved cases.	
	Number.	Per cent.	Number.	Per cent.
Negative	56	52	9	38
Direct positive (jaundice)	29	27	8	33
Indirect alone positive (latent jaundice)	23	21	7	29

TABLE 11.—VERIFIED COMPLICATING LESIONS IN 250 CASES.

Heart disease:		Duodenitis	1
Myocardial (with symptoms)	13	Carcinoma, primary, in duodenal wall	1
Chronic valvular	2	Gastric polyp	1
Appendicitis:		Diabetes mellitus	4
Acute	1	Hypertension	4
Chronic	6	Syphilis	2
Liver disease:		Renal calculus	1
Hepatitis	6	Pyelonephritis	1
Catarrhal cholangitis	2	Toxic goiter	1
Carcinoma (primary)	1	Colitis	1
Duodenum:			—
Ulcer	3		52
Diverticulum	1		

Complicating Diseases. This group of cases is too small to offer evidence of value in determining the diseases most likely to be associated with cholecystitis. It does, however, bear out the impression widely held, and recently put in tabular form by Rivers and Hartman,[10] of the high proportion of coincident disease. The

proved coexisting lesions among these 250 individuals were divided among 13 disease groups, and occurred in more than one-fifth of the cases (21 per cent). Myocardial disease with symptoms was perhaps more frequent here (5 per cent) than among the population at large of similar age range.

Follow-up. The figures of the results of surgical treatment, included by courtesy of Drs. Müller and Eliason, on whose services the patients underwent operation, are included simply to indicate the type of result to be expected from conservative surgery in contrast to the known poor result of any medical therapy.

TABLE 12.—FOLLOW-UP, 4 MONTHS TO 3 YEARS, ON 50 PATIENTS WITH OPERATIVELY PROVED GALL BLADDER DISEASE.

	Well.	Improved.	Unimproved.	Died.
Cholecystectomies, 43.				
Cholecystitis	3	1	1	2
Stones in gall bladder	21	7	2	0
Stones in common duct	2	0	2	2
Totals	26	8	5	4
Cholecystostomies, 7.				
Cholecystitis	0	2	0	0
Stones in gall bladder	3	2	0	0
Totals	3	4	0	0

Conclusions. 1. The diagnostic procedures in gall bladder disease which have proved of most value in this clinic are, in order of their effectiveness in 250 instances: (1) A careful and complete history and physical examination; (2) cholecystogram; (3) gastrointestinal roentgenography; (4) duodenal drainage; (5) the van den Bergh test and icterus index; (6) fractional gastric analysis.

2. Gastrointestinal roentgenography can be made of more positive value in diagnosis of cholecystic disease than is the case at present.

3. Duodenal drainage can be made effective in diagnosis by very careful routine technique and examinations to be made only by a thoroughly trained person, preferably a physician. Otherwise the procedure is not worth the time and effort involved.

4. While each one of these procedures will not be needed in every instance of suspected biliary disease, together, if carefully done, they are adequate to give in the doubtful case sufficient data to warrant decision for or against laparotomy.

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THE PERSONALITY TYPE OF PATIENTS WITH ARTERIOLAR ESSENTIAL HYPERTENSION.

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It has long been believed that patients with arteriolar essential hypertension have special physical and emotional reactions to life—in other words, that such patients have a special type of personality. If this is true, then the knowledge and application of this fact may not only aid the diagnosis and therapy of this disease, but may afford insight into its etiology. Unfortunately, the evidence for this idea of a special hypertensive type consists almost wholly of clinical impressions. It has been the purpose of the present investigation to test the validity of these clinical impressions by controlled study.

Literature. In accord with many writers on this aspect of the subject, Mosenthal[1] states that arteriolar (essential) hypertension "occurs rather more frequently in the highstrung, nervous, or irritable individual." Likewise O'Hare[2] says that "almost all have been of a nervous temperament throughout life." Herrick[3] believes that hypertensive patients have an "ill-balanced personality" whose chief tendencies are "pressure of activity and over-earnestness." He says further that they are "serious, earnest, conscientious, enthusiastic at work, at their infrequent play, and too often at table." Barach[4] finds that early in life hypertensive patients have "a certain instability, restlessness, a lack of confidence and shirking of responsibility . . . During middle life . . . they frequently are restless or ineffectual, or they may be abnormally active and intensive in their special field of endeavor." Moschcowitz[5] has presented one of the most detailed and interesting descriptions of the hypertensive type. He has observed among other things that "the greatest proportion of patients with hypertension are terribly tense and pursue their vocation with tremendous seriousness, and

worry over trivialities. In consequence, they are irritable. They are the antithesis of the child. They do not play. They have no time for play. They have narrow intellectual horizons." In general, the above writers believe that hypertensive patients tend to be highstrung, serious, and overactive.

Several physicians have tried to verify these valuable clinical impressions by more exact studies. O'Hare, Walker and Vickers[6] analyzed the records of 300 hypertensive patients whose average age was 51 years. They found that 42 per cent had one or more of the following symptoms in their early history: "Frequent epistaxis; abnormal flowing at menstruation; migraine; cold, sweaty, and cyanotic hands; flushing; blushing; extreme sensitiveness; a highstrung and nervous temperament, etc. In 100 of these hypertensive patients who were questioned especially for these symptoms, we were able to establish their presence in 87 per cent." By contrast, in 436 patients with normal blood pressures whose average age was 36 years, these "symptoms of vasomotor weakness, etc., were noted in only 23 per cent" of the records analyzed. On the other hand, the studies of Patek and Weiss[7] showed no striking differences in personality between a group of 47 hypertensive patients and 37 patients with normal blood pressure. On questioning their patients they found that 67 per cent of the hypertensive patients were "excitable" as compared with 54 per cent of the control group; 75 per cent of the hypertensive patients were "hyperactive" as compared with 65 per cent of the control group; 53 per cent of the hypertensive patients were "impulsive" as compared with 37 per cent of the control group; and 83 per cent of the hypertensive patients "worried excessively" as compared with 54 per cent of the control group. Thus, the only definite "difference between the two groups was in their relative propensities to worry."

Neither of these studies offers adequate proof for or against the existence of a special hypertensive personality. O'Hare, Walker and Vickers studied the psychic and vasomotor reactions of only the early life of hypertensive patients, without inquiring into the reactions of these patients during their later years. Furthermore, the average age of the control group was 15 years less than the average age of the hypertensive group so that many in this younger control group might develop hypertension in the following 15 years. In the study of Patek and Weiss, no mention is made of the age of their patients other than that both groups had "similar age distribution." Most important, they do not state the method of questioning their patients or the questions asked. This information is essential in evaluating their results. It is easy to obtain affirmative answers from the majority of people who are asked, for example, "Are you sensitive?"; a much smaller number will respond in the affirmative to the question "Are you unusually sensitive?"; while a still smaller number will give positive answers to the question, "In

general, have you been more sensitive than the average person?" In neither of the above studies was mention made as to what was considered normal blood pressure. Both of the studies were carried out on ward patients and, therefore, many of the normal patients may easily have had mild hypertension which dropped to normal during bed rest or during inactive ward life.[8] Furthermore, in both of the studies, the control cases were sick ward patients. Therefore, these control patients were not healthy normal people, but sick patients with normal blood pressure. The above studies really constitute a comparison of the personality type of hypertensive patients with the personality types of patients with peptic ulcer, bronchial asthma, tuberculosis, carcinoma, etc., who had normal blood pressure. Diseases like peptic ulcer, for example, may possibly occur in people of certain personality types,[9] so that the personalities in the control groups of the above studies are not those of a truly normal group of people. The literature, therefore, indicates the need of further study of the personality in hypertensive patients.

Clinical Material of Present Study. The clinical material used in the present study consisted of 182 ambulatory "patients" seen in dispensary and private practice. The details of age, sex, weight, blood pressure, etc., of these patients are presented in Table 1. The standards of normal blood pressure used in this study are those of Rogers and Hunter.[11] The subjects fall into the following 5 clinical groups:

TABLE 1.—CLINICAL MATERIAL OF PRESENT STUDY.

Groups.	Number of patients.	Number of females.	Average age of group, yrs.	Range in age.	Range of systolic blood pressure, mm. of Hg.	Range of diastolic blood pressure, mm. of Hg.	Average weight of group above normal standard for age and height, in pounds.*
1 . .	41	28	54	36 to 74	160 to 280	90 to 160	14.7
1a . .	20	11	56	39 to 67	160 to 260	92 to 158	7.0
2 . .	34	12	26	15 to 35	150 or more in 50% 140 or more in 80%	90 or more in 33%	11.3
3 . .	35	12	47	36 to 71	130 or less in 75% 130 to 140 in 25%	less than 90 in 86% 90 to 100 in 14%	8.0
4 . .	52	17	25	15 to 35	130 or less in all 124 or less in 70%	80 or less in all 70 or less in 50%	5.5

* See No. 10 in bibliography.

Group 1. Middle-aged hypertensive patients with symptoms.

Group 1a. Middle-aged, symptom-free, hypertensive patients. Most of the patients in Groups 1 and 1*a* had secondary cardiac enlargement and retinal vascular changes, while a few had mild secondary renal damage.

Group 2. Young hypertensive individuals. Twenty-one of the patients in this group made two or more visits, and 50 per cent of those seen on a second visit still had abnormally high systolic pressures. Only 2 patients continued to have abnormally high diastolic blood pressures at the second visit. Twenty-five of the subjects in Group 2 were children of parents with definite essential hypertension, were symptomless, and had not requested medical attention. The parents had been examined by the author.

Group 3. Middle-aged control subjects with normal blood pressure. Most of the patients in this group were either healthy people who wished a general examination, or ambulatory people referred for general medical examinations because of uncomplicated gonorrhea, obesity, skin diseases, primary syphilis or varicose veins. All of these patients had few if any symptoms.

Group 4. Young control subjects with normal blood pressure. Twenty-seven of the 52 patients were referred for general medical examinations because of uncomplicated gonorrhea or skin diseases. They had few, if any, symptoms. The remaining 25 subjects were children of parents with definite essential hypertension, were symptomless, and had not requested medical attention. Their parents had been examined by the author.

Method of Present Study. The same specifically worded direct questions in regard to personality were asked of the control subjects and the patients with hypertension. There was no hesitancy by the author of employing direct questions because both control and hypertensive subjects were subjected to the same method of questioning. This method of allowing the subject to evaluate his own personality is considered very satisfactory when dealing with nonpsychotic individuals who have no reason to conceal anything. Only subjects who readily grasped the questions were utilized. It was a striking fact that the great majority of people were able to give a prompt reply to the questions asked. It might be argued that hypertensive patients may possibly be more introspective than subjects with normal blood pressure. This possible error was found to be absent, for, on inquiring in many cases among the intimate relatives of the subjects, the relatives agreed that the subjects evaluated their personality quite accurately. Each subject was questioned in such a way as to avoid as far as possible being influenced by the tone of the questioner. In about 20 per cent of the subjects the personality study was made before the blood pressure reading was determined. The questions selected referred partly to personality characteristics commonly mentioned in the literature as associated with hypertension, and partly to personality traits with which I personally have been impressed in hypertensive patients.[12] The entire study, including determinations of the blood pressure, was carried out by the author. The blood pressure was determined by the mercury sphygmomanometer and auscultation. The end of the third phase was the criterion of diastolic blood pressure. The complete list of the questions as they were asked is as follows:

1. In general, throughout your life, not on any one special occasion, and compared to the average person of your own age with whom you have come in contact, have you been of an unusually highstrung nature or of a calm nature?

2. In general, throughout your life, not on any one special occasion, and compared to the average person of your own age with whom you have come in contact, have you been the sort of person who loses his temper quickly (who flies off the handle easily over little things) or has it usually required a good deal to make you lose your temper?

3. In general, throughout your life, not on any one special occasion, etc. . . . (as in Question 2) . . . have you been the sort of person who even if you don't show it externally, feel yourself frequently getting all excited over little things?

4. In general, etc. . . . (as in above questions) . . . have you been the sort of person whose feelings are unusually easily hurt, who is unusually sensitive, or does it take a great deal to make you feel hurt?

5. As a younger person did you or do you still blush or flush unusually easily compared to the average person your age? Would people "kid you about it?"

6. As a younger person, did you or do you still become unusually easily embarrassed compared to the average person?

7. In general, etc. . . . have you been the sort of person who worries unusually easily over little things, or have you tended to pass them over?

8. In general, etc. . . . (as in Questions 1 and 2) . . . have you been of an unusually serious nature or of a happy-go-lucky nature?

9. In general, etc. . . . have you been of an unusually forward or unusually shy nature?

10. In general, etc. . . . have you ever had frequent nosebleeds?

11. In general, etc. . . . have your hands or feet tended to become easily cold on slight changes in weather?

12. In general, etc. . . . have you tended to walk at an average pace, slower than the average person, or faster than the average person?

13. In general, etc. . . . have you tended to work at an average pace, slower than the average person, or definitely faster than the average person?

14. In general, etc. . . . have you tended to eat or talk at an average rate, slower than the average person with whom you eat (or talk) or faster than the average person.

15. In general, etc. . . . have you been of average, less than average, or more than average physical activity?

Only definite replies were used, so that when a patient stated that he could not definitely answer, that particular patient was not credited with any reply to that special question. Where the patient stated that a particular trait had existed in him for only a few years rather than his whole life, he was credited as not having that trait throughout his life, that is, from the point of view of the present study, that trait was absent most of his life.

Results. The results of the questioning are presented in Tables 2 and 3. Let us temporarily omit a consideration of the selected Group 1*a*. It is seen that 52 per cent of both the older and the younger hypertensive persons (Groups 1 and 2) stated that they were unusually highstrung their whole life, compared to only 3 and 6 per cent of the corresponding control groups (3 and 4). Of the older group, 43 per cent, and of the younger, 53 per cent stated that they were unusually quick tempered their whole life, compared to only 3 and 13 per cent for the replies of the corresponding control groups. Of the older group, 69 per cent, and of the younger, 66 per cent said that they were unusually sensitive their whole life, compared to 9 and 18 per cent for the replies of the corresponding control groups. Of the older group, 70 per cent, and of the younger, 58 per cent said they worried unusually easily over little things their whole life, compared to only 11 per cent of the corresponding control groups. Of the older patients, 94 per cent, and of the younger, 69 per cent said that, compared to the average person their own age, they were definitely more active physically their whole life, compared to 13 and 10 per cent for the answers of the corresponding control groups. This unquestionable preponderance of high percentages among the hypertensive groups is seen also in the answers to practically all the other questions (Table 2).

Referring to Table 3 it is seen that the frequency of the various

traits in the hypertensive patients becomes exceedingly high when the replies to two or more questions are added together. Thus, for example, 97 per cent of the older and 70 per cent of the younger hypertensive patients said they were either unusually highstrung, or unusually active, or both, compared to 7 and 15 per cent for the replies of the corresponding control groups. This was one of the outstanding correlations of the entire study. Further correlations of combined questions are seen in Table 3.

TABLE 2.—PERCENTAGE INCIDENCE OF CERTAIN PERSONALITY CHARACTERISTICS IN SUBJECTS WITH HYPERTENSION AND WITH NORMAL BLOOD PRESSURE.

Group No.	Blood pressure.	Average age.	Number of patients.	Unusually highstrung.	Unusually quicktempered.	Unusually easily excited within themselves.	Unusually sensitive.	Unusually easy blushing.	Unusually easy embarrassment.	Unusually easy worrier.	Unusually serious.	Unusually shy.	Unusually fast walker.	Unusually fast worker.	Unusually fast talker or eater.	Unusually active physically.	Frequent epistaxis.	Hands or feet easily cold.	Family history of vascular disease.
1	H*	54	41	52	43	54	69	65	48	70	59	70	58	87	64	94	2	13	71
1*a* . . .	H	56	20	30	25	25	25	35	35	30	50	..	60	65	50	70	..	..	40
2 . . .	H	26	34	52	53	64	66	38	44	58	61	58	58	79	68	69	6	17	77
3 . . .	N	47	35	3	3	6	9	21	23	11	19	44	29	33	28	13	6	11	25
4 . . .	N	25	52	6	13	12	18	25	11	11	23	21	29	29	24	10	0	20	62

* Abbreviations in all the tables are the same. H = hypertension. N = normal.

TABLE 3.—PERCENTAGE INCIDENCE OF CERTAIN PERSONALITY CHARACTERISTICS IN SUBJECTS WITH HYPERTENSION AND WITH NORMAL BLOOD PRESSURE.*

Group No.	Average age.	Number of patients.	Unusually highstrung or quicktempered, or easily excited within themselves.	Unusually quicktempered or sensitive.	Unusually serious or sensitive.	Unusually sensitive or quick worker.	Unusually quicktempered or quick worker.	Unusually highstrung or active.	Unusually easy blushing or shyness.	Unusually quick-tempered, or sensitive, or serious or active.
1 . .	54	28	68	77	85	93	94	97	90	90
1*a* . .	56	20	50	40	60	80	70	75	..	80
2 . .	26	28	76	74	81	90	80	76	70	
3 . .	47	31	3	9	25	36	30	7	39	35
4 . .	25	46	12	29	35	41	36	15	33	

* Figures obtained by adding together the positive replies to two or more questions.

Turning next to Group 1*a* in Table 2, consisting of the specially selected, symptomless hypertensive subjects, it is first seen that to

every question there was also a definitely higher percentage of positive answers than in both control groups. However, compared to the other hypertensive groups (1 and 2), Group 1*a* had a much lower number of positive answers to the questions dealing with the emotional responses such as quick temper and sensitiveness. On the other hand, to the questions relating to physical activity, the symptomless hypertensive patients gave almost as high a percentage of positive answers as the other hypertensive groups.

Discussion. The present study confirms the often mentioned clinical impression that persons with arteriolar (essential) hypertension tend to have certain emotional and physical reactions much more frequently and intensely than comparatively healthy people of the same age group and with normal blood pressure—in the present study from 2 to 17 times as commonly as do the normal controls (Tables 2 and 3). The results confirm the author's previous impressions that hypertensive patients tend to be emotionally hyperactive, physically hyperactive, or both. In presenting and discussing the statistical data in Tables 2 and 3, the author has had only one purpose—to indicate trends rather than immutable statistics. Thus, the results in Tables 2 and 3 indicate that hypertensive patients tend to be highstrung individuals who either display quick temper or are easily excited within themselves. They tend to be unusually sensitive, being hurt by little things. In youth and often persisting to later life, they tend to blush easily, to be easily embarrassed, and to be unusually shy. In dealing with the events of life, however minute, they tend to be unusually serious and worry over trivialities. However, as seen in Table 2, a much smaller percentage of the symptomless hypertensive patients admit that they are emotionally hyperactive, although this percentage is definitely greater than in the control group. Physically, whether symptomless or not, the hypertensive individual seems to be an unusually rapid walker, even when in no special hurry. Hypertensive subjects tend to work at their tasks in home or in office with much more rapidity and thoroughness than the average person. They often tend to eat or talk rapidly. In general, they tend to be unusually active physically, in their domestic, occupational, and social activities. It cannot be too strongly emphasized that the author does not believe that every person with a hypertensive type of personality has or will develop arteriolar (essential) hypertension. Neither is it meant that every hypertensive patient has the type of personality above presented. It is clear, however, that most hypertensive patients in the groups studied are of the personality type described.

The Hypertensive Personality is of Lifelong Duration. Not only does the middle-aged hypertensive patient tend to be of a certain personality type, but the replies indicate that so far as he can remember he has always been of that type. It seems likely, there-

fore, that the hypertensive personality is present and recognizable in early life. This likelihood is further confirmed by the study of the younger hypertensive group, which already at an average age of 26 shows exactly the same type of personality reactions to life as the older group. The probability that most of the persons in our younger group with abnormally high blood pressure readings are cases of early arteriolar (essential) hypertension, is enhanced not only by the finding in them of a similar type of personality as in the older hypertensive patients, but also by the significant fact that about 80 per cent of them are the children of known hypertensive patients.

Differentiating the Hypertensive Personality from Other Types. It is important to distinguish the hypertensive personality from that present in anxiety-neurosis with normal blood pressure and in the manic-depressive type of individual. Thus, it is well known that hyperactive emotional responses are present in many nonhypertensive people who undergo marked emotional strain. In such people the emotional strain may cause not only hyperactive emotional responses, but also bodily symptoms—in other words the picture of the psychoneuroses. However, the difference between the hyperactive emotional responses of the hypertensive patients and of the psychoneurotic patients is usually one of duration—the personality type of the hypertensive person being lifelong, whereas in most psychoneurotics it is only as long as the existence of the emotional upset.[13] Yet there are many psychoneurotic patients of almost lifelong duration. It is obvious, therefore, that a study such as this must try to avoid the use of subjects who have symptoms of psychoneuroses, or take account of it.

Therefore, as a control for this factor the personality of a group of symptom-free hypertensive individuals was studied. This group of 20 persons gave no history of symptoms suggesting psychoneurosis. They prided themselves on being unusually well all their lives and of practically never going to doctors. If it is true that many of the symptoms of hypertensive patients are due to emotional disturbances,[13] it would seem likely that symptom-free hypertensive "patients" should have a less frequent incidence of traits associated with emotional instability than hypertensive patients with symptoms. This is exactly what was found in Group 1*a*. In these 20 symptomless hypertensive patients, only 30 per cent stated they were unusually highstrung compared to 52 per cent in the hypertensive patients with symptoms; 25 per cent said they were unusually quick-tempered, easily excited, or unusually sensitive, compared to 53, 64 and 66 per cent respectively in the symptom group. However, the hyperactive physical responses in the symptom-free group were as frequent as in the other hypertensive groups studied.

The hypertensive personality is quite different from that of the

neurasthenic individual. The latter, as a rule, may be emotionally hyperactive for a period, but is not physically hyperactive. He fatigues easily—one of the outstanding characteristics of the neurasthenic. He may want to do a great deal, but is unable to do so physically, which is in direct contradistinction to the hypertensive type.

The hypertensive personality must be distinguished also from the manic-depressive type. There are many people who will say that they are of the hypertensive type but have no hypertension. Many of these people, however, are of a manic-depressive type of personality without being psychotic. They have a great deal of physical energy and enthusiasm, but it is not a constant thing. Akin to the actual manic-depressive psychoses, they have periods in which they are unusually energetic, often lasting for months or more, followed by periods of depression during which their activity is much less. The hypertensive patient, however, has a drive within him which is persistent, steady, and not broken up by periods of depression. However, one cannot be dogmatic; for, mixed types often occur, and a hypertensive patient may have a depression.

Etiology of the Hypertensive Personality. This matter is unsettled. Moschcowitz[5] believes it may be of environmental acquired origin, "the result of imitative tendency of children," which gives a pseudo-hereditary aspect to it. Against the environmental etiology of the hypertensive personality are 25 of the young control individuals in Group 4, who, although they are the children of hypertensive patients and they have lived in the environment of these parents and of their hypertensive brothers and sisters, have neither the hypertensive personality nor elevated blood pressure like their brothers and sisters. Barach,[4] on the other hand, believes the hypertensive personality is primarily the result of physical influences, like the personality changes in myxedema, hyperthyroidism, or eunuchoidism. It is highly possible that the hypertensive personality is of physical, perhaps endocrine origin. Certain it must be, in the light of the present study, that the hypertensive personality, present as it is early in life, can be neither the result of any unusually high blood pressure, nor the result of secondary vascular disease. It is also unlikely that it is due to environmental imitation of parents.

Relation of the Hypertensive Personality to the Diagnosis of Essential Hypertension. The recognition of the hypertensive personality may be of definite aid in the diagnosis of arteriolar (essential) hypertension. Given a patient in whom the diagnosis of chronic vascular nephritis secondary to arteriolar hypertension is difficult to separate from a diagnosis of chronic glomerular nephritis with hypertension, the absence of the hypertensive personality is one more bit of evidence in favor of the primary kidney disease, rather than the hypertensive origin. The hypertensive personality type may also be of

aid in the diagnosis of early arteriolar hypertension; for, given a young person with mild fluctuating hypertension, the presence of the hypertensive personality, especially in the presence of a positive family history of vascular disease, strongly supports the diagnosis of early arteriolar essential hypertension rather than simple emotional hypertension. I believe that it is here that the knowledge of the hypertensive personality has one of its greatest applications—the early diagnosis of this disease. One may go even still further and say, as O'Hare[14] has, that the presence of vasomotor instability (and I would add the hypertensive type of personality) in children of a hypertensive patient, even before the existence of hypertension, calls for prophylactic measures.

The Hypertensive Personality in Treatment of Arteriolar Essential Hypertension. Elsewhere I have described[12] the importance of attempting to modify the hypertensive personality in the treatment of arteriolar essential hypertension. The relation of the hypertensive personality to the production of early symptoms has already been discussed,[13] so that therapy of early symptoms must take account of this fact. Suffice it here to say, that it is well known that the hyperactive emotional and physical responses of the hypertensive patient are accompanied by marked elevations in blood pressure. Therefore, any rational therapy of arteriolar essential hypertension must attempt to modify this personality, either by education, sedatives, or both.

Finally, it is sincerely hoped that the present study will stimulate further investigation of the hypertensive personality by specially trained students of personality.

Summary and Conclusions. 1. A simple study of the personality of 182 subjects has been made. These subjects consisted of middle-aged hypertensive patients, hypertensive patients between the ages of 18 to 35, middle-aged normal subjects with normal blood pressure, and young normal subjects with normal blood pressure.

2. The results indicate that hypertensive subjects tend to have a distinct type of personality. Their personality is characterized by increased psychomotor activity. They are dynamic, hyperactive individuals, with a large and steady output of energy. They tend to be sensitive and quick-tempered. The mood fluctuations, however, are not an important feature, which differentiates them from the manic-depressive individuals. The hypertensive personality has existed as far back as the subject can remember.

3. The relation of the hypertensive personality to the diagnosis and treatment of arteriolar essential hypertension is discussed.

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THE FRACTIONAL PHENOLSULPHONEPHTHALEIN TEST IN BRIGHT'S DISEASE.

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Since the introduction of the phenolsulphonephthalein test of kidney function by Rowntree and Geraghty[9] the method commonly used has been the estimation of the dye excreted in specimens of urine collected 1 and 2 hours after injection. The value of this test in severe nephritis has been generally recognized. However, Christian and O'Hare[3] and others have observed that this test fails to reflect the impaired function in moderate or slight degrees of nephritis, and they place more reliance on the 2-hour concentration test. In cases of mild or suspected nephritis Bowen[2] found the phenolsulphonephthalein test less informative than tests of urea excretion. Van Slyke, McIntosh, *et al.*[13] have recently concluded that the urea clearance test shows diminution of renal function before the phenolsulphonephthalein test.

Rowntree, in 1910, stated that the "curve of elimination of phenolsulphonephthalein in nephritis differs from the normal in that the maximum intensity is slowly reached." Later Snowden[12] noted that the earliest indication of impaired renal function was a delay in the excretion of dye. Thus a patient with Bright's disease may have a total output of 60 per cent in 2 hours with only 30 per cent appearing in the first hour, whereas in the normal person 50 per cent appears in the first hour. In 1925 Shaw[11] determined the

normal curve of dye elimination by collecting urine at 5- and 15-minute intervals after intravenous injection and found that an average of 40 per cent of the dye appeared in the first 15 minutes. He applied this technique of fractional collections to cases of renal disease and found marked abnormalities in the curve of excretion in many cases where the 2-hour output was normal. A decreased output in the first 15 minutes or a delay in the peak of elimination was frequently the only evidence of kidney disease.

It is surprising that this important modification has had clinical application, to our knowledge, only in urologic surgery. We have employed Shaw's method of frequent collections, which we have called the *fractional phenolsulphonephthalein test*, in order to determine whether or not it gives a better indication of kidney function in Bright's disease than the usual method of hourly collections, and also to determine its comparative value with the urea clearance test.

The Excretion of Phenolsulphonephthalein in Normal Individuals. Chart 1, Fig. 1, indicates the variations of the curve of phenolsulphonephthalein excretion which we have obtained from 40 tests on 20 normal individuals ranging in age from 11 to 40 years. Two tests were done on each at an interval of several days. The subject voided, drank 600 cc. of water and after 30 minutes 1 cc. (6 mg.) of phenolsulphonephthalein was injected intravenously. Voided specimens of urine were then collected at intervals of 15, 30, 45, 60 and 120 minutes. Estimations of the per cent of dye excreted were made with a Duboscq colorimeter, using standards freshly prepared with phenolsulphonephthalein.

Except for the slightly lower average 15-minute output, this curve (Fig. 1) is similar to that described by Shaw. Seven initial readings were above 40 per cent and 3 were below 30 per cent. Eight individuals who doubled their fluid intake on the second test showed no greater variation in their curve than those on a constant intake. This agrees with the findings of Rowntree and Shaw but not with those of Sugimura,[10] who noted an increase of about 5 per cent in the first 30 minutes' excretion while the subjects were forcing fluids.

Snowden has stated that the excretion of phenolsulphonephthalein is definitely increased in severe nephritis when the urine volume is increased. To estimate the effect of an increase in urine volume on the output of dye by such diseased kidneys we have repeated the fractional phenolsulphonephthalein tests on 4 patients with Bright's disease while they were forcing fluids. Under these conditions we find no significant changes in the dye output.

The Fractional Phenolsulphonephthalein Test in Bright's Disease. In the past 2 years we have used this test in a large number of patients with suspected renal disease. From this group we have selected all cases with a clinical diagnosis of Bright's disease in whom both the fractional phenolsulphonephthalein and the urea

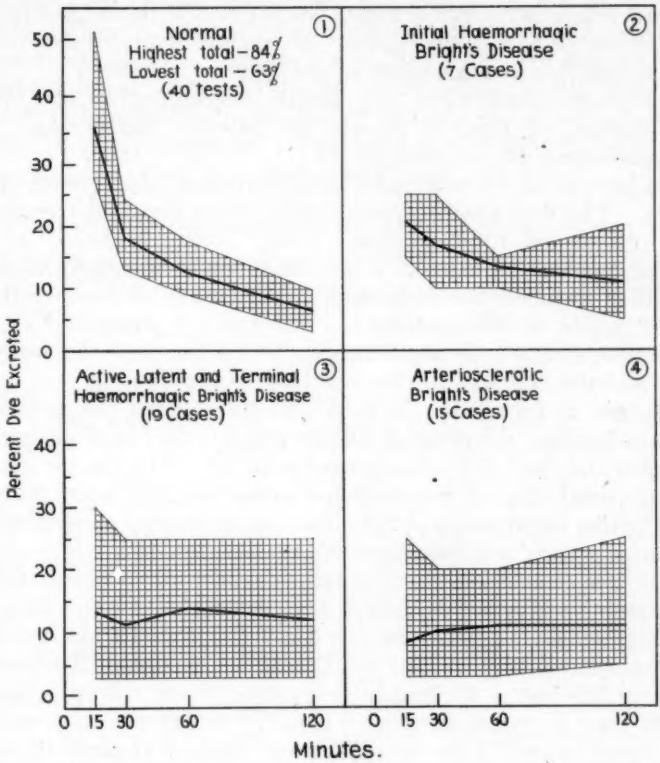

FIG. 1.—The variations and the average curve of phenolsulphonephthalein excretion in normal persons and in those with Bright's disease.

TABLE 1.—THE RELATION OF URINE VOLUME TO THE OUTPUT OF DYE BY DISEASED KIDNEYS.

No.	Fluid intake, cc.	Fractional 'phthalein. Per cent dye. Minutes. 15	30	60	120	Total.	Total urine volume, cc.	Date.
32	400	10	10	..	25	45	275	2- 4-32
	1200	5	10	15	12	42	770	2-15-32
36	400	10	5	10	5	30	175	2-12-32
	1500	10	5	10	15	40	545	2-15-32
22	400	5	3	5	5	18	410	2-15-32
	1600	5	5	10	10	30	1275	2-16-32
17	600	10	5	10	15	40	170	4-25-32
	2000	15	5	5	12	37	785	4-27-32

clearance tests were performed. No patients with congestive cardiac failure or with extrarenal factors, such as liver disease,[4] or the recent ingestion of magnesium sulphate* were included.

Forty-three such cases are grouped according to the Addis classification of Bright's disease[1] as follows: hemorrhagic, 26; arteriosclerotic, 15; degenerative, 2.

We have divided hemorrhagic Bright's disease into 2 groups in the tables. The first group corresponds to acute glomerular nephritis and the second to the chronic form. Arteriosclerotic Bright's disease includes all cases in which the lesion is essentially vascular and thus includes the malignant hypertension of comparatively young people, of which there are 7 cases in our group of 15. Degenerative Bright's disease corresponds to lipoid nephrosis, amyloidosis and the nephritis of chemical and toxic poisoning.

Analysis of Data.—In the tables we have listed the significant urinary findings, the range of specific gravity, the blood non-protein nitrogen and the 2 tests done on each patient. The specific gravity was obtained in most instances from concentration tests, but in a few, further information of the ability of the kidney to concentrate the urine was gained from single urine examinations.

The urea clearance tests were performed according to the method described by Moeller, McIntosh and Van Slyke.[7] The values for the 2 specimens of urine usually checked within 10 per cent and corrections for body weight[8] were made for children. The normal range of this test in the standard clearance (where the urine volume is less than 2 cc. per minute) is from 76 to 121 per cent, so that any figure below 76 per cent indicates diminished renal function. In the maximum clearance (where the urine volume is above 2 cc. per minute) the normal range lies between 85 and 132 per cent.

The fractional phenolsulphonephthalein tests were done as part of the routine laboratory work, using Hynson, Westcott and Dunning standards, and the same technique was used as described for the normals except that the patient drank 400 to 500 cc. of water and the 45-minute specimen was omitted. Only occasionally was a patient unable to void at the stated intervals. No normal person excreted less than 28 per cent of dye in the first 15 minutes, but we have taken 25 per cent as the lowest limit of normal in the patients. Although the lowest total output in 2 hours in the normal group was 63 per cent, we have considered 55 per cent as normal in our analysis of cases for two reasons: (1) This is generally accepted; (2) Van Slyke *et al.* used this figure in their comparison of the urea clearance with the phenolsulphonephthalein test.

Analysis shows that there is some agreement of the range of specific gravity and the non-protein nitrogen with the urea clearance

* Macht[6] has shown that the ingestion of magnesium sulphate delays the elimination of phenolsulphonephthalein, the effect lasting 3 to 4 hours after ingestion.

and fractional phenolsulphonephthalein tests. In the 43 cases we find that the specific gravity was below 1.024 in 21, the non-protein nitrogen was above 40 mg. per 100 cc. in 25, the urea clearance test indicated impaired renal function in 29 cases and the fractional phenolsulphonephthalein in 35. Inasmuch as we are primarily interested in the fractional phenolsulphonephthalein and the urea clearance tests, we shall consider only these two.

TABLE 2.—INITIAL HEMORRHAGIC BRIGHT'S DIEASE.

(Cs Indicates Standard Urea Clearance; Cm Indicates Maximum Urea Clearance.)

No.	Sex, age.	Urine.				NPN.	Fractional 'phthalein.						Urea clearance, per cent of normal av.	
							Per cent excreted.							
							Minutes.				Total.	Date.		Date.
		Alb.	R.B.C.	Casts.	Range of sp. gr.		15.	30.	60.	120.				
1	F 37	+ +	+++ ○	+ ○	1.010 1.018	32	25 30	10 18	15 15	10 10	60 73	5-16-31 5-24-32	51% Cm 94% Cs	5-25-31 6-10-32
2	M 15	+++	++	+	1.010 1.028	41 27	20	25	15	15	75	3-19-31	144% Cm	3-18-31
3	M 6	++	+++	+++	1.012 1.024	46 39	20	25	15	..	60 (1 hr.)	5-28-31	42% Cs	5-27-31
4	M 14	++++ ++++	++++ ++++	++++ +++	1.014 1.026	27 35	20 20 17	25 20 23	15 10 15	5 5 ..	65 55 55 (1 hr.)	1-27-32 2-19 32 7-22-32	135% Cs 135% Cs 116% Cm	1-29-32 2-25-32 7-22-32
5	M 43	++ ++	+++ +	++++ ++	1.010 1.034	85 35	20 25 23	15 15 25	15 13 15	12 10 10	60 63 73	5-27-30 6-18-30 7-17-30	48% Cs 47% Cm	5-28-30 6-24-30
6	M 15	+	++	+++	1.003 1.024	34 23	20	15	15	20	70	12-19-30	107% Cs	12-18-30
7	M 14	++++ ○	++++ +	++ +	1.010 1.020	104 60 34	15 30	10 15	10 ..	5 ..	40 45 (½ hr.)	11-1-31 11-15-31	90% Cs 122% Cs	11-2-31 11-18-31

In Table 2 (initial hemorrhagic Bright's disease) the first 6 of the 7 cases had an output of phenolsulphonephthalein of at least 55 per cent in 2 hours. This would be considered normal if it were the only information we had concerning the excretion of the dye. However, using the fractional method, we find that there is a delay in the elimination of the dye, which we interpret as indicating diminished kidney function, in all of these except Case 1, whose 15-minute excretion was 25 per cent. In only 3 of the 6 (Nos. 1, 3, 5) did the urea clearance indicate impaired function. In 1 case (No. 1) the urea clearance alone indicated diminished function, but a year later both tests gave higher values.

Case 7, a boy, aged 14 years, entered the hospital in convulsions. Both the fractional phenolsulphonephthalein and the urea clearance

tests, performed several days later when he was able to coöperate, were below the normal variations. Two weeks later when he was clinically improved and albuminuria had disappeared, both tests had returned to normal.

TABLE 3.—ACTIVE, LATENT AND TERMINAL HEMORRHAGIC BRIGHT'S DISEASE.

No.	Sex, age.	Urine.				NPN.	Fractional 'phthalein.						Urea clearance, per cent nf normal av.	
							Per cent dye.							
							Minutes.				Total.	Date.		Date.
		Alb.	R.B.C.	Casts.	Range of sp. gr.		15.	30.	60.	120.				
8	M 49	+++ ++	++++ +++	++ ++	1.005 1.019	40 ...	25 25 25	25 .. 15	15	10 .. 15	75 ... 55	1-10-32 1-14-32 7-1-32	130% Cm 98% Cs	1-14-32 7-11-32
9	F 33	+++	+	+	1.018 1.024	26	25	20	20	10	75	6-12-32	76% Cs	6-14-32
10	M 50	+++	+	++++	1.015 1.024	29	25	15	15	5	60	11-1-31	85% Cs	11-10-32
11	M 40	++++ ++++	++ ++	++++ ++++	1.018 1.026	35	30 8	10 12	10 18	10 15	60 53	12-9-31 6-3-32	93% Cs 53% Cs	12-10-31 7-1-32
12	M 26	++++	+++	++	1.010 1.020	26	20	15	15	15	65	10-10-30	39% Cs	11-6-30
13	F 38	O +	+ O	+ O	1.006 1.025	53 46	10 20	10 10	20 20	25 ..	65 50 (1 hr.)	5-16-31 8-19-32	51% Cm 92% Cs	5-21-31 9-9-32
14	F 15	++++	+	+++	1.012 1.022	39 59	10	15	15	20	60	12-19-30	50% Cs	12-19-30
15	F 27	+	+	O	1.002 1.014	72 41	15	..	25	15	55	3-20-31	23% Cm	4-6-31
16	F 14	++++	+	+++	1.008 1.024	35	10	15	15	15	55	12-27-31	51% Cs	12-24-31
17	M 53	++++	+	+	1.016 1.022	36 ..	15 10 8	13 5 12	15 10 15	15 15 ..	58 40 35 (1 hr.)	4-21-32 4-25-32 6-20-32	80% Cs 104% Cm	4-22-32 7-1-32
18	F 20	++++ ++++	++ +	++++ ++	1.010 1.030	29 ..	15 5	15 10	15 15	.. 15	45 (1 hr.) 45	12-16-31 7-7-32	77% Cs 91% Cs	12-2-31 7-8-32
19	F 22	++	O	+	1.010 1.018	44	17	10	15	..	37 (1 hr.)	6-4-32	50% Cs	6-6-32
20	M 30	+++	++++	++++	1.010 1.024	48 31	3	5	25	10	43	3-19-32	89% Cs	3-9-32
21	F 15	++++	+	++++	1.014 1.032	25 44 63	5	5	8	8	26	11-2-31	41% Cs	12-9-31
22	F 25	++	+	+	1.010 1.020	38 ..	3 5	5 3	3 5	8 5	19 18	1-22-32 2-15-32	44% Cm	2-3-32
23	F 59	++++	O	++++	1.012 1.024	60 50	3 ..	3 ..	3 ..	3 ..	12	11-29-31	18% Cs Died	12-2-31 9-10-32
24	F 44	+	+	+++	1.010 1.014	95 70	0 ..	0 ..	0 ..	0 ..	0	6-17-31	19% Cs Died	6-10-31 7-13-31
25	M 23	++++	++	++++	1.010 1.020	70 ..	5 ..	5 ..	5 ..	10 ..	25	9-21-31	18% Cs Died	10-14-31
26	M 17	++++	+	++	1.008 1.015	180 ..	0 ..	3 ..	3 ..	3 ..	9	3-11-32	8% Cs Died	3-14-32 4-14-32

The tests in Case 4 are interesting because the patient entered in the initial stage and progressed into the active chronic stage with persistence of hematuria and albuminuria. During this time 3 comparative tests were done. The fractional phenolsulphonephthalein tests showed progressive impairment whereas the urea clearance remained normal.

TABLE 4.—ARTERIOSCLEROTIC BRIGHT'S DISEASE.

No.	Sex, age.	Urine.				NPN.	Fractional 'phthalein.						Urea clearance, per cent of normal av.	
							Per cent dye.							
							Minutes.				Total.	Date.		Date.
		Alb.	R.B.C.	Casts.	Range of sp. gr.		15.	30.	60.	120.				
27	F 35	+	○	○	1.006 1.020	37 27	25 ..	20 ..	20 ..	15 ..	80	5-27-31	57% Cs Died	5-27-31 3-3-32
28	F 29	+++ +++	○ ○	++ ○	1.010 1.030	59 ..	8 tr	15 3	8 5	20 5	51 15	11-30-30 6-27-32	59% Cs 35% Cs	12-1-30 6-27-32
29	F 67	++	++	+++	1.010 1.018	76 60	15	10	15	10	50	5-14-31	52% Cs	5-15-31
30	M 50	+	○	+	1.018 1.028	38	12	15	15	10	52	11-3-30	65% Cs	11-5-30
31	F 36	++	○	++	1.013 1.020	25	8	20	10	10	48	11-11-30	79% Cm	11-17-30
32	M 38	+++	+	++	1.010 1.016	36 65	15 10 3	.. 10 3	20 .. tr	10 25 5	45 45 10	1-29-32 2-4-32 3-22-32	63% Cs 35% Cm Died	2-4-32 3-22-32 6-1-32
33	F 50	++	○	○	1.006 1.020	83 50	5	10	15	15	45	3-14-31	31% Cs	3-16-31
34	M 47	+++	+	+	1.012 1.024	45 64	5	15	10	10	40	1-17-31	72% Cs	1-13-31
35	F 22	+++	+	+	1.008 1.025	22 ..	10 ..	5 ..	10 ..	10 ..	35	10-9-30	37% Cs Died	10-10-30 12-13-30
36	F 45	+++	+	○	1.001 1.016	46	5	5	5	10	25	6-14-32	70% Cs	6-13-32
37	F 32	+++	○	+	1.010 1.020	64 ..	3 ..	3 ..	3 ..	5 ..	14	2-5-32	39% Cs Died	2-8-32 7-22-32
38	M 40	+++	+	++	1.008 1.024	47 59	10 ..	5 ..	10 5	5 13	30 18	2-12-32 4-2-32	122% Cs 67% Cs Died	2-15-32 4-5-32 6-27-32
39	F 41	++	+	+	1.012 1.024	36 ..	15 ..	15 ..	10 ..	15 ..	55	10-29-30	50% Cs Died	11-12-30 3-31-31
40	F 55	++	+	++++	1.014 1.020	66 ..	3 ..	.. ..	5 ..	5 ..	13	12-16-31	15% Cs Died	12-21-31 3- -32
41	F 49	+++	+	++	1.009 1.012	130 ..	3 ..	0 ..	3 ..	3 ..	9	12-14-31	7% Cs Died	12-14-31 5- -32

From Table 3 we find that the first 10 patients (Nos. 8 to 17) had at least 55 per cent output in 2 hours; 6 of these (Nos. 12 to 17) showed abnormal fractional tests, with a delay in the excretion

of dye. The remainder of the group (Nos. 18 to 26) all showed rather marked kidney impairment by the fractional test and the total output was well below 55 per cent. In all except 3 of the patients (Nos. 17, 18, 20) both the urea clearance and the fractional phenolsulphonephthalein tests agreed. In these only the latter test indicated a diminished function. We have been able to repeat the tests at intervals of several months on Patients 8, 11, 13, 17 and 18. In Patient 8 the tests were normal on both occasions, although albuminuria and hematuria were still present at the second examination. The first fractional phenolsulphonephthalein and urea clearance tests were normal on Patient 11, although at that time the patient had considerable edema, albuminuria and a blood pressure of 160 systolic and 100 diastolic. Six months later both tests showed a marked decrease. The total output in the dye test was very little changed, but the fractional readings showed a great difference with a low initial output and a delayed excretion. In Patient 13 both tests showed improvement after a year's interval. Patient 17 showed a slight decline in the fractional test alone. Patient 18 showed a decrease in the fractional phenolsulphonephthalein but the urea clearance increased 14 per cent. Clinically this patient was worse and was having persistent edema to the midthighs at the time of the second test.

Of the patients with arteriosclerotic Bright's disease (Table 4) only 2 (Nos. 27, 39) had a total output over 55 per cent. In Patient 39 the excretion of dye was delayed, but in Patient 27 it was normal by the fractional test, yet the urea clearance showed an impaired function.

TABLE 5.—DEGENERATIVE BRIGHT'S DISEASE.

Case 42.—Diagnosis: amyloidosis; tuberculosis of the cecum.
Case 43.—Diagnosis: bichlorid of mercury nephrosis.

No.	Sex, age.	Urine.				N P N.	Fractional 'phthalein.						Urea clearance, per cent of normal av.	
							Per cent dye.							
							Minutes.				Total.	Date.		Date.
		Alb.	R.B.C.	Casts.	Range of sp. gr.		15	30	60	120				
42	M 25	++++	0	++++	1.008 1.022	24 ..	15 19	.. 10	30 ..	15 ..	60 20 (½ hr.)	12-12-31 12-18-31	102% Cs	12- 7-31
43	M 39	++	0	+	1.005 1.024	30 ..	15 20	35 35	15 17	.. 3	65 75	5-28-32 6-3-32	96% Cs	5-31-32

Comparative tests done after a lapse of months in Patients 28 and 32 showed a diminished kidney function by both tests, although a greater diminution was reflected by the fractional phenolsulphone-

phthalein. In Patient 38 the urea clearance test at the first period of study showed a high normal but a very low fractional phenolsulphonephthalein test. Two months later the patient became much worse and the urea clearance was reduced one-half. He died shortly thereafter.

The effect of a high blood pressure on the excretion of phenolsulphonephthalein remains an unsettled problem. Lundsgaard and Moeller[5] believe that the dye output may be decreased in the presence of a high blood pressure. We have encountered patients with hypertension without congestive failure who had depressed curves of phenolsulphonephthalein excretion but with few or no other signs of kidney disease. However, we have observed normal fractional phenolsulphonephthalein tests in as many patients with hypertension in whom there was no evidence of Bright's disease.

In Table 5 are listed the 2 cases of degenerative Bright's disease. In both of these there was a delay in the elimination of phenolsulphonephthalein, yet the total output of the dye and the urea clearance were normal.

Discussion. In summing up we find that 14 patients (32.5 per cent) with a total dye output of 55 per cent or more had a delay in the elimination of phenolsulphonephthalein. This group represents cases that would be judged to have a normal excretion of dye by the old method of hourly collections, but this delay shown by the fractional method indicates a diminished renal function. The charts in Fig. 1 show the variations and the average curve of dye excretion in normal persons and in those with Bright's disease. As the renal lesion progresses it is apparent that the curve tends to flatten out.

In a comparative study of the urea clearance test with the 2-hour output of phenolsulphonephthalein after intravenous injection, Van Slyke *et al.* have shown that when the urea clearance is between 40 and 60 per cent of normal average function about one-half the phenolsulphonephthalein outputs are above and one-half below 55 per cent of the dye injected. We find this to be true of our cases, but an analysis of the 8 cases (Nos. 1, 3, 5, 13, 14, 16, 27, 39) with the phenolsulphonephthalein output above 55 per cent and the urea clearance between 40 to 60 per cent shows that all but 2 (Nos. 1, 27) had a delayed excretion of dye indicating impairment of kidney function and thus agreeing with the urea clearance test. On the other hand, there were 9 patients (Nos. 2, 4, 6, 17, 18, 20, 38, 42, 43) in whom the urea clearance was 76 per cent or above and yet the fractional phenolsulphonephthalein test showed a diminished function.

Of the 12 patients in whom repeated tests were done later in the course of their disease we find that 5 (Nos. 7, 11, 13, 28, 32) had approximately parallel changes in both the urea clearance and the

fractional phenolsulphonephthalein tests. In 3 (Nos. 4, 17, 18) a decrease in the kidney function of patients with active hemorrhagic disease was shown only by the phenolsulphonephthalein test. In 2 (Nos. 1, 5) the urea clearance gave a better indication of the changes in function. In 1 (No. 8) both tests were normal.

It is particularly significant, on review of all cases, that an abnormal elimination of the dye was reflected chiefly in the first 15-minute specimen, and so this is by far the most important. For the general practitioner and in the out-patient department this determination alone would be sufficient in most cases. It is, of course, essential to know that there is no urinary retention and that the patient has completely emptied the bladder. Finally it should be emphasized that the fractional phenolsulphonephthalein test is a simple procedure, not requiring the aid of a chemical laboratory, and in our experience is more practical than the urea clearance test.

Summary and Conclusions. The fractional method of estimating the elimination of phenolsulphonephthalein (15, 30, 60 and 120 minutes) has been studied in the past 2 years in 20 normal subjects and a large number of patients with suspected renal disease.

We have found that in Bright's disease the fractional test may show evidence of impaired renal function when the test as usually done, with hourly collections, is interpreted as normal.

This fractional test is quite as informative as the urea clearance test and reflects the diminishing function in progressive kidney disease.

Since it is easier to perform, it is the method of choice for routine clinical work.

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NORMAL VARIATIONS IN RENAL FUNCTION TESTS WITH DISCUSSION OF THEIR PHYSIOLOGIC SIGNIFICANCE.

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In order to estimate the value of kidney function tests in renal disease it is important to know what function of the kidney each test measures and how great a departure from normal must occur before abnormal function can be revealed. Most tests in clinical use today are able to indicate at best gross damage to the kidney, and physicians make little attempt to separate them according to the type of disturbed kidney physiology. Albuminuria, for example, is due to a different physiologic mechanism than is an inability of the kidney to concentrate urine, but both abnormalities frequently are interpreted as signs of nephritis without thought as to their underlying cause.

One great obstacle to the scientific classification of renal function tests is the delay in accepting the Ludwig theory of urine formation of filtration through the glomeruli with a reabsorption of fluid and solids in the tubules, as set forth by Cushny[1] and verified by the direct observations of Richards and his colleagues.[2] According to this theory, which we have adopted as a working hypothesis, in the glomeruli a process of filtration takes place whereby all of the constituents of the blood plasma except the proteins pass into the glomerular filtrate in the same concentration as they exist in the plasma. As this filtrate passes down the tubules most of the water is reabsorbed into the blood. The solid waste elements of the filtrate return through the tubular walls in greater or less extent. Thus creatinin, to which the tubular cells are apparently impermeable, probably is not appreciably reabsorbed, whereas about 50 per cent of the urea is reabsorbed. Certain substances present in the plasma, however, normally appear in the urine either not at all or in less concentration than in the plasma. These elements, such as glucose and chlorids, known as threshold substances, cannot be reabsorbed in the tubules by a simple process of back diffusion, but by a specific activity of the tubular cells.

In order to account for the degree of concentration of some of the substances in the urine of man, Rehberg[3] has calculated that a

glomerular filtration of from 100 to 200 cc. per minute is necessary. Since the urinary output under normal conditions rarely exceeds 1 to 2 cc. per minute, it is obvious that about 99 per cent of the water may be reabsorbed by the tubules. To estimate the amount of glomerular filtration Rehberg employs creatinin as an index, since there is indirect evidence that little or none of this substance is reabsorbed in its passage down the tubules. If the concentration of creatinin in the blood and urine and the urinary excretion per minute are known, then, as creatinin concentration in the glomerular filtrate and plasma is identical,[2] the ratio of the percentage of urine creatinin to plasma creatinin represents the degree to which the glomerular filtrate is concentrated. This value is known as the *concentration index*. The amount of glomerular filtrate formed per minute is, therefore, equal to this concentration index times the urinary excretion and can be determined from the formula:

$$\text{Glomerular filtrate} = \frac{\text{urinary concentration creatinin}}{\text{plasma concentration creatinin}} \times \text{urine formed per minute.}$$

Under abnormal conditions, alterations in the formation of urine may occur from disturbances of: (1) filtration and (2) reabsorption. In studying the function of the kidneys clinically, it is desirable to obtain a separate estimate of these two functions. Filtration may be lessened by: (*a*) Diminution in the glomerular blood pressure; (*b*) a decrease in permeability of the glomerular membrane; or (*c*) a reduction in cross-sectional area of the filtering surface due either to damage to individual glomeruli or to a reduction in the total number of glomeruli. Reabsorption of fluid may be lessened either because of an increased volume of filtrate flowing down the tubule or as a result of damage to the tubular cells.

Clinical Methods for Determining Altered Renal Function. 1. *Glomerular Function.* The creatinin clearance procedure of Rehberg gives a direct indication of the amount of glomerular filtration. The urea clearance test under conditions of maximal excretion also gives a relative index of the degree of filtration, since with urinary excretions exceeding 2 cc. per minute the percentage of back diffusion of urea through the tubules is nearly constant. When the urea and creatinin clearance are performed simultaneously, it is possible to compute the percentage of urea reabsorbed by the tubules and thus detect any increased permeability which may occur.

In the advanced stages of renal disease the glomerular filtration is so much decreased that the kidneys are unable to maintain an adequate excretion of nitrogenous and other waste products. These substances are, therefore, found in abnormally high concentration in the blood plasma. In clinical practice the usual tests are for the total nonprotein nitrogen, urea nitrogen, creatin, creatinin and uric acid of the blood.

The presence of albumin in the urine indicates an abnormal permeability of the glomerular membrane to protein, and the presence of red blood corpuscles is due either to increased permeability or to rupture of capillaries. Casts are found as the result of inflammatory changes and are due to the coagulation of protein and cells which have passed into the lumina of the tubules.

2. *Tubular Function.* The ability of the tubules to reabsorb water is best measured by procedures which concentrate the urine to as high a degree as possible. The capacity of the tubular cells to absorb threshold substances actively can be examined by estimating the concentration of one or more of these solids in the blood and urine.

Purpose of Investigation. In order to correlate a study of several simultaneously applied clinical technical procedures with the physiologic functions which they estimate and to show how fluctuation in one test may affect the outcome of other tests, we have studied a group of normal young adults, none of whom had albuminuria or an abnormal urinary sediment.

Methods. The subjects were in a fasting state and remained in bed throughout the test periods except when the concentration tests were made.

(*a*) *Creatinin Clearance.* The technique of Rehberg[3] with unimportant modifications was followed. Three grams of creatinin were fed 1½ hours before the urine collection period began. The plasma creatinin was determined by the method of Folin and Wu[4] using picric acid purified according to Benedict's directions.[5] The urine creatinin was determined by Folin's method.[6] The calculation of the glomerular filtrate was made according to the formula previously stated. The values for plasma creatinin found in the samples taken before and after each hourly test period were averaged.

The terms "creatinin clearance" and "urea clearance" have been employed, because such a term was suggested by Van Slyke for the urea procedure and we have used his formulæ in expressing our values. The "creatinin clearance" is synonymous with the term "glomerular filtrate."

(*b*) *Urea Clearance.* This was usually determined simultaneously with the creatinin clearance. The analyses for urea were carried out on whole blood and urine by Van Slyke's gasometric extraction method.[7]

The urea clearance per minute when the urinary excretion exceeded 2 cc. per minute was calculated from the same formula as creatinin, substituting urea for creatinin. Seventy-five cc. was taken as the theoretical normal. This is called the "maximum clearance."

When the diuresis falls below 2 cc. per minute Van Slyke and his coworkers[8] have suggested that the formula is best expressed by taking the square root of the urinary minute volume rather than the total urinary minute volume. This determination is called the "standard clearance." In the few cases (Table 1) where the diuresis fell below 2 cc. per minute, the actual urea clearance values were calculated from the formula for maximal clearance for the sake of uniformity. In these cases, however, figures for the percentage of normal in the same table were calculated from the standard clearance formula, taking 54 cc. as the theoretical normal.

(*c*) *Concentration Test.* A modification of the Volhard and Strauss tests for the concentration and dilution of urine similar to that suggested by Pratt[9] was employed. The only fluid permitted was 1500 cc. of water

at the beginning of the test. The output in the first 4 hours, the total day and the total night outputs were determined and the specific gravities of the individual samples were measured.

TABLE 1.—THE VALUES OF THE CREATININ AND UREA CLEARANCES OBTAINED IN NORMAL INDIVIDUALS.

Subject.	Age.	Urine, cc. per min.	Creatinin.		Urea.			Blood urea nitrogen, mg. per cent.
			Conc. index.	Filtrate, cc. per min.	Clearance, cc. per min.	Per cent of normal.	Excretion,* per cent.	
1	31	0.76	179	136	56	118†	38	10.2
		1.40	89	125	69	108†	52	
2	44	2.42	60	135	61	81	39	15.2
		7.00	22	154	67	90	40	
3	31	4.75	36	172	112	149	60	7.4
		8.00	17	136	119	158	81	
4	22	8.93	17	154	70	93	42	9.0
		11.05	14	153	77	102	46	
5	41	0.40	301	120	34	99†	26	11.8
		2.25	57	129	70	94	51	
6	34	1.50	108	162	64	119†	44	11.5
		4.28	42	180	96	128	50	
7	26	2.17	67	145	68	91	43	9.0
		8.26	15	122	54	73	40	
8	38	7.50	16	117	48	64	37	7.9
		11.00	7	79	66	85	79	
9	35	7.09	20	141	80	108	53	15.6
		9.16	14	125	92	122	68	
10	29	1.28	125	160	64	105†	37	10.3
		3.50	49	170	81	108	43	
11	29	3.78	43	164	100	134	57	11.0
		4.67	31	146	98	130	61	
12	45	7.33	30	220	109	145	46	7.9
		6.57	29	180	97	129	47	
13	22	1.63	...	...	70	102†	..	8.9
		8.33	...	...	69	82	..	
14	24	5.66	...	...	63	85	..	13.2
		9.47	...	...	58	77	..	

* Calculated according to Rehberg,[3,14] corrected for plasma urea nitrogen.

† Per cent of normal calculated by formula for "standard clearance" $= \frac{U\sqrt{V}}{B}$. All the other per cents of normal are on a basis of "maximum clearance" $= \frac{U\ V}{B}$.

Results. *Creatinin and Urea Clearance.* Creatinin and urea clearance tests were carried out simultaneously in 12 subjects (Table 1). The creatinin filtrate varied from 117 to 220 cc. per minute with one exception probably due to technical error. These figures are in accord with Rehberg's and average slightly less than those given by Cope[10] for 1 normal male.

In the same 12 subjects and in 2 more, urea clearance measurements were made. These varied from 48 to 119 cc. per minute. When expressed in terms of percentage of normal, assuming a maximum clearance of 75 and a standard clearance of 54 to be nor-

mal, the figures ranged from 64 to 158 per cent. In the cases with a clearance of 64 and 73 per cent, second determinations, respectively, showed 85 and 91 per cent of normal.

Although a rough parallelism was found to exist between the levels of the creatinin and urea clearance, this did not hold with any exactitude. Most of the discrepancy probably was due to the experimental error of the methods, but it is quite possible that fluctuations were caused by individual variations which permitted the urea to diffuse in different proportions back through the tubules to the blood.

Our observations are in agreement with Rehberg that the glomerular filtrate measured by the creatinin test is essentially constant irrespective of the urine volume. This constancy also holds for the urea clearance when the diuresis exceeds about 2 cc. per minute, as has been noted by Van Slyke.[8] When, however, the diuresis falls below this rate the percentage excretion of urea becomes progressively less, with a consequent decrease in the urea clearance. Our observations also suggest that the percentage excretion of urea varies between individuals even under identical conditions.

In order to ascertain whether the oral administration of urea or creatinin increased the urea clearance values, 9 subjects were tested. The results (Table 2), in accord with those of Addis and Drury,[11] indicate that there is no tendency for either urea or creatinin to increase the urea clearance, or, by inference, the creatinin clearance either. There was some fluctuation in the consecutive hourly determinations in spite of the maintenance of conditions as constant as possible. This is particularly marked in Subject 19. In only 4 instances did the urinary output fall below 2 cc. per minute. This low urine output accounts for the low clearance values found in Subject 7 when urea was fed.

It is desirable in the carrying out of both the creatinin and urea clearance procedures in clinical practice to have conditions made as constant as possible. That is, an adequate diuresis of at least 2 cc. per minute should be insured by having the subject drink 400 cc. or more water each hour before and during the test periods. The patient should be kept quiet in bed and preferably should be in the fasting condition.

Concentrating Power of Tubules. Dilution concentration tests were carried out in 5 subjects (Table 3). Even with normally functioning kidneys the results may be modified by such factors as the position and activity of the individual, the degree of hydration or dehydration and the elimination of fluid by other channels. It is probable that one or more of these factors was responsible for the lack of urine dilution below a specific gravity of 1.007 in Subject 15, and for the failure of 3 of the 5 subjects (Nos. 10, 17 and 18) to excrete all or nearly all of the 1500 cc. of water ingested within 4 hours. For clinical purposes, however, the value of this

test consists not so much in the total urinary output or the hourly variation in it as it does in the range of specific gravity through which the urine varies and particularly in the maximum specific gravity to which the individual can concentrate urine. It is this that shows the capacity of the tubules to reabsorb water. Practically all normal individuals can concentrate urine to a specific gravity of 1.025 or more.

TABLE 2.—THE EFFECT OF FEEDING CREATININ AND UREA ON THE UREA CLEARANCE OF NORMAL INDIVIDUALS.

Subject.	Urea clearance. Nothing fed. cc. per min.	Creatinin fed 3 gm. cc. per min.	Urea fed 30 gm. cc. per min.	Urine, cc. per min.
10	76	...	...	5.3
	80	...	...	4.9
		64	...	1.3
		81	...	3.5
			80	3.0
			77	5.7
12	102	...	...	3.8
	100	...	...	12.5
		109	...	7.3
		97	...	6.6
			92	2.3
			89	3.5
19	116	...	...	7.7
	73	...	...	2.3
		93	...	5.4
		77	...	2.5
			123	11.0
			83	6.8
11	93	...	...	12.1
	75	...	...	7.5
		98	...	4.7
		100	...	3.8
13	70	...	...	1.6
	69	...	...	8.3
			65	5.0
			60	12.3
			57	12.3
7	...	68	...	2.2
		54	...	8.3
			36	1.0
			38	0.9
8	...	48	...	7.5
		66	...	11.0
			62	9.0
			62	13.6
9	...	80	...	7.1
		92	...	9.2
			111	10.9
			83	12.0
			85	11.2
14	...	63	...	5.7
		58	...	5.7
			57	4.4
			52	9.5
			48	8.8

TABLE 3.—THE RESULTS OF DILUTION-CONCENTRATION TESTS IN 5 NORMAL INDIVIDUALS, SHOWING VARIATION IN URINE OUTPUT, SPECIFIC GRAVITY, CONCENTRATION INDEX AND GLOMERULAR FILTRATE.

Subject.	Age.	4-hour output, cc.	Day output, cc.	Night output, cc.	Total output, cc.	Specific gravity.		Concentration index.		Filtrate.	
						Lowest.	Highest.	Lowest.	Highest.	Lowest, cc.	Highest, cc.
10	29	685	925	410	1325	1.001	1.036	10	226	26	97
15	33	1030	1580	220	1800	1.007	1.030	16	243	74	180
16	25	1225	1390	285	1675	1.001	1.033	8	270	54	102
17	33	850	1190	340	1530	1.001	1.031	10	160	65	120
18	28	965	1220	380	1600	1.002	1.026	11	137	54	89

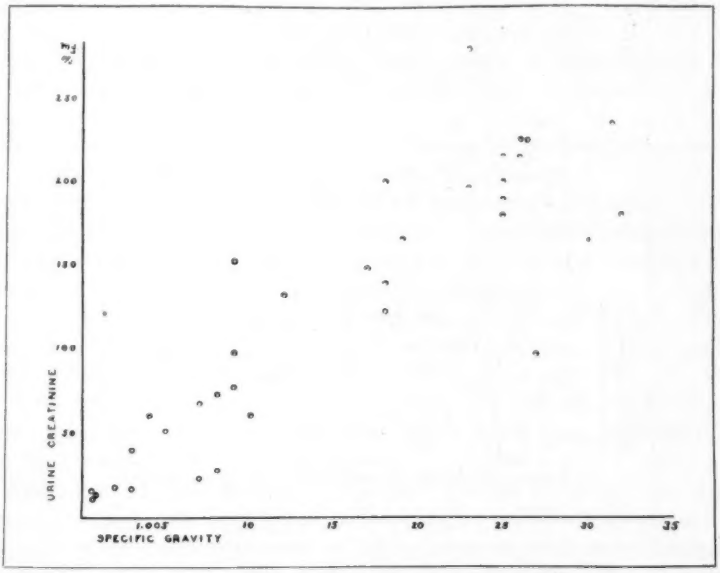

CHART I.—The relationship of the variation in urine specific gravity and creatinin concentration in normal individuals.

Daily Variation in Glomerular Filtrate. In conjunction with the dilution-concentration test, the glomerular filtration during each of the collection periods was calculated to ascertain what changes took place when urine was passed which varied from extreme dilution to marked concentration. No creatinin was fed. Only 1 blood creatinin determination was made in each subject. There is evidence that the percentage variation of the plasma creatinin in the same individual at different times is slight.[12] The relationship of the creatinin concentration in the urine to its specific gravity is

depicted in Chart I which shows that these two factors bear practically a linear relationship to each other. That is, under normal circumstances the specific gravity of the urine varies in direct proportion to the amount of creatinin present.

The low values obtained for the glomerular filtrate, we believe, are due largely to the experimental error in determining plasma creatinin at normal levels. Not only is it impossible to determine with accuracy the normal amount of plasma creatinin, but it is quite likely that the results obtained yield values in excess of the true amount.[3,10,13] There is also some evidence that the glomerular filtrate tends to be somewhat higher when the subject is in the prone than in the upright position.[14]

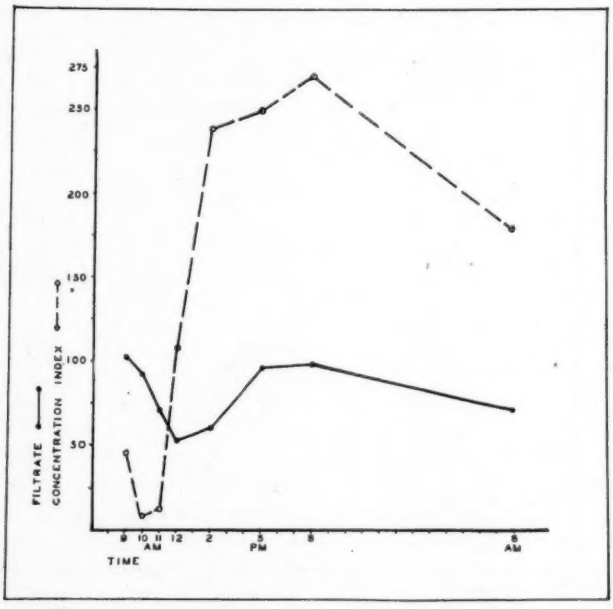

CHART II.—The diurnal variation of glomerular filtrate and of the concentration index during a dilution-concentration test in Subject 16.

Chart II and Table 3 show the relative constancy of the glomerular filtrate when compared with the change in concentration and amount of urine which was noted by Fremont-Smith[15] and others. In other words, the variation in the amount of water excreted and in the concentration of urine is controlled largely by the extent of the reabsorption of water in the tubules.

Clinical Application of Renal Function Tests. No single technical procedure is adequate to test thoroughly the function of the kidney. Assuming the correctness of the filtration-reabsorption theory of

renal activity, it is possible to gain information concerning the following processes:

1. Permeability of glomeruli.
2. Glomerular filtration.
3. Tubular reabsorption of fluid.
4. Return of solids through the tubules into the plasma.
5. The "vital" reabsorption of threshold substances.

Except under unusual circumstances there is little value in testing the fourth and fifth processes in cases of inflammatory or vascular nephritis because rarely are they markedly abnormal. However, each of the first three kidney processes should be examined.

Information is gained regarding the permeability of the glomeruli by examination of the urine for albumin, red corpuscles and casts.

The urea or creatinin clearance tests are indices of glomerular filtration. Either test can be employed clinically. It should be appreciated that the reliability of the final results in these procedures is as much dependent on the accuracy in the collection of all the urine passed over an accurately timed period as on the laboratory analysis.

The tubular reabsorptive power is shown by concentration tests of which that of Volhard is a representative example.

Determination of phenolsulphonphthalein excretion is unquestionably valuable to show gross renal change. Examination of the blood for the abnormal retention of nitrogenous and other elements is of value only in the advanced stages of renal disease.

These laboratory procedures are of value only in supplementing clinical observation. They supply worthwhile information only when conducted with care under controlled conditions, and the results obtained require careful interpretation. Moreover, the tests must be repeated frequently if knowledge is to be attained regarding the progression of the disease process.

Summary and Conclusions. 1. On 12 normal subjects urea and creatinin clearance tests were performed and on 5 subjects dilution concentration tests were carried out. These studies were made to show the normal variations of each test and the effect of changes in one test on the others, and to correlate the results with the physiologic functions of the kidney which they measure.

2. The creatinin clearance test probably gives a close estimate of the absolute degree of glomerular filtration and the urea clearance provides a relative index of this function. Clinically, either test may be used.

3. The ability of the renal tubules to reabsorb fluid is best measured by a concentration test.

4. To attain as adequate an estimate as is possible by laboratory methods regarding the state of renal function, the tests mentioned together with an ordinary examination of the urine will suffice.

5. At best the information gained from these procedures merely supplements that obtained by the actual clinical observation of the patient.

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THE RENAL FUNCTION IN PERSONS WITH ONE KIDNEY.

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The present study concerns the degree of renal function in 12 patients who had undergone unilateral nephrectomy, in 9 of whom the remaining kidney was presumably normal. Such a study, it was hoped, might give information as to (1) the degree of impairment of renal function occasioned by removal of one kidney, and (2) the extent of reduction in functioning kidney tissue which must occur before such a reduction could be detected by laboratory tests.

Material Studied.—Nine of the 12 patients, 5 men and 4 women, complained of no symptoms and showed no abnormalities of the cardiovascular renal systems. They were from 16 to 50 years of age. None showed albuminuria or abnormality of the urinary sediment. The operative removal of the kidneys was because of pyonephrosis, hydronephrosis, calculus, tumor or trauma. Three of the cases were studied within 2 weeks of the time of operation and again 4 to 5 months later. In 1 of these patients the kidney was almost completely destroyed by hydronephrosis; but in the other 2, 1

of whom had a tumor and the second a congenital anomaly, the renal tissue, although somewhat reduced in amount, was apparently normal in quality and possessed functioning ability. The remaining 5 cases had had nephrectomies performed from 18 months to 6 years previous to the observations. Of the 3 who suffered from complications 2 had pyonephrosis involving the remaining kidney, and the third had hypertension.

The technique of the renal function procedures carried out is described in the preceding paper.[1] The urea and creatinin clearance values were determined simultaneously. A modification of Volhard's dilution-concentration test was employed, and the excretion of phenolsulphonphthalein 130 minutes after its intramuscular injection was estimated.

Results. The cases have been divided into 5 groups. The division between the 3 groups of longstanding cases without complications is dependent on very slight differences in the results of one or more of the functional tests, but has been made because it facilitates analysis in regard to the physiologic and compensatory changes.

GROUP 1. *Recent Cases.* Tests were performed on Cases 1 and 2 within 2 weeks of operation (Tables 1 and 2). Gross and microscopic examination of the removed kidneys indicated that the renal tissue, although somewhat reduced in extent, possessed functioning ability. In both patients the glomerular filtrates determined by the creatinin method were at the lower limit of normal and the urea clearances were reduced to a parallel extent. In these subjects the maximum concentrating power of the kidneys was possibly slightly diminished. The total fluid excretion was normal and the phenolsulphonphthalein excretion was excellent. In both patients the examinations were repeated 4 to 5 months after the operation. The results obtained were almost identical to those obtained shortly after operation.

GROUP 2. *Cases With Normal Kidney Function.* In 2 cases (3 and 4) the functional tests were normal (Tables 1 and 2). In Case 3 the kidney was removed 20 months previously. The second patient was studied 2 weeks and again 4 months postoperatively, but since the removed kidney was almost entirely destroyed by hydronephrosis, it is reasonable to assume that he had had but one functioning kidney for some time. For this reason it is doubtful how much, if any, of the improvement which is evident from the tests should be ascribed to compensatory hypertrophy of the intact kidney following operation.

GROUP 3. *Cases With Questionable Diminution of Concentrating Ability.* All tests on Cases 5, 6 and 7 were normal except that the patients were unable to concentrate their urine above a specific gravity of 1.020, 1.022 and 1.024 respectively (Tables 1 and 2).

GROUP 4. *Cases With Disturbed Filtration.* Two cases (8 and 9) had glomerular filtrates, as calculated by the creatinin clearance test, below the lower limit of normal, 100 cc. per minute (Tables 1 and 2). In these subjects, however, the urea clearance values and the concentrating power of the kidneys were normal.

TABLE 1.—THE UREA AND CREATININ CLEARANCES, THE BLOOD UREA NITROGEN, AND THE PHENOLSULPHONPHTHALEIN EXCRETION IN 12 PATIENTS WITH ONE KIDNEY.

Patient.	Age.	Arterial blood pressure, mm. Hg.	Duration of nephrectomy.	Diagnosis.	Phthalein excretion, per cent.	Urea.		Blood urea nitrogen, mg. per cent.	Creatinin filtrate, cc. per min.	
						Clearance, cc. per min.	Per cent of normal.			
1	16	118/80	8 days	Congenital anomaly of renal pelvis	70	54	72	8	91	No complications
						54	72	..	102	
			5 weeks		..	52	70	10	98	
						44	59	..	81	
			5 months		75	56	75	8	113	
						56	75	..	86	
2	24	115/80	2 weeks	Tumor	65	30*	56	9	132	
						50	67	..	75	
			4 months		70	56	75	9	105	
						46	62	..	103	
3	50	134/84	20 months	Pyonephrosis	45	95	127	13	163	
						92	102	..	180	
4	18	120/80	2 weeks	Hydronephrosis	50	71	95	8	..	
						66	89	..	..	
			4 months		65	95	127	10	157	
						95	127	..	112	
5	42	108/76	18 months	Trauma	50	72	96	13	113	
						66	88	..	105	
6	40	112/70	4 years	Pyonephrosis	45	81	107	5	142	
						75	100	..	132	
7	23	114/74	1 year	Calculus	65	75	100	15	128	
						53	70	..	113	
8	27	110/68	4 years	Pyonephrosis	35	65*	121	18	70	
						66*	122	..	65	
9	43	120/80	6 years	Calculus	75	72	96	12	76	
						70	93	..	90	
10	47	130/85	12 years	Pyonephrosis	..	24	32	14	37	Complications
						20	26	..	34	
11	52	126/76	18 months	Pyonephrosis	20	31*	58	15	56	
						26*	48	..	57	
12	44	230/135	9 years	Pyonephrosis	..	39	52	18	66	
						32	43	..	57	

* Urea clearance expressed in terms of "standard" clearance of Van Slyke. All others are "maximum."

TABLE 2.—THE RESULTS OF THE DILUTION-CONCENTRATION TEST IN THE PATIENTS WITH ONE KIDNEY, SHOWING THE URINE EXCRETION AND THE VARIATION IN SPECIFIC GRAVITY, CONCENTRATION INDEX AND GLOMERULAR FILTRATE.

Subject.	4-hour output, cc.	Day output, cc.	Night output, cc.	Total output, cc.	Specific gravity.		Concentration index.		Filtrate.		Time since operation.	
					Lowest.	Highest.	Lowest.	High'st.	Lowest, cc. per min.	High'st, cc. per min.		
1	1100	1370	235	1605	1.002	1.024	7	164	36	54	5 weeks	No complications
	1220	1485	180	1665	1.001	1.024	..	...	..	...	5 months	
2	1140	1500	190	1690	1.001	1.021	..	...	..	...	2 weeks	
	1320	1520	180	1700	1.001	1.023	..	...	..	...	4 months	
3	1130	1414	355	1770	1.002	1.026	11	210	64	195	20 months	
4	1270	1724	541	2265	1.001	1.020	..	...	..	...	2 weeks	
	1210	1735	330	2065	1.001	1.025	9	170	78	108	4 months	
5	740	1232	520	1750	1.002	1.020	17	178	52	78	18 months	
6	incomplete		190	....	1.002	1.022	8	189	49	133	4 years	
7	812	1133	340	1473	1.001	1.024	8	128	41	112	1 year	
8	507	649	89	738	1.002	1.040	7	265	22	66	4 years	
9	1100	1375	310	1685	1.002	1.025	8	120	45	57	6 years	
11	556	incomplete			1.003	1.011	..	...	..	....	18 months	Complications
12	734	1194	325	1519	1.003	1.021	8	55	23	44	9 years	

GROUP 5. *Cases With Complications.* The 3 patients (Cases 10, 11 and 12) suffering from complications had had nephrectomies performed previously for pyonephrosis. In 2 of the cases the symptoms and large amounts of pus and albumin in the urine gave evidence that the infection had involved the remaining kidney. In these cases the pathologic process had involved the remaining kidney to an extent sufficient to result in a marked interference with renal function as indicated by the laboratory procedures.

The third patient (Case 12), a man, aged 44 years, on whom a nephrectomy had been performed 9 years previously, had had a known hypertension for 8 years, with gradually increasing cardiac symptoms. All functional tests of his kidneys gave low results. His urine contained much albumin.

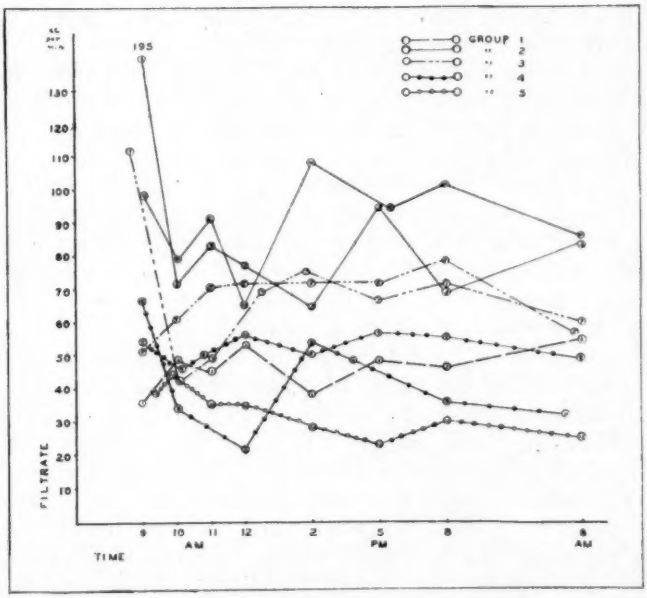

CHART I.—The diurnal variation in glomerular filtrate during a dilution-concentration test in 9 individuals with one kidney.

Daily Variation in the Filtrate. In 9 of the cases the glomerular filtrate was determined throughout a 24-hour period in conjunction with the dilution-concentration tests (Chart I). No creatinin was fed during these examinations. The level of the filtrate determined in this way tended to be lower than that obtained by creatinin clearance tests when the same patients were fed creatinin. The probable cause for this finding, observed also in normal persons, has been discussed previously.[1] The glomerular filtrate remained relatively constant compared to the degree of concentration of the

various urine specimens. Thus in persons with one kidney, as in normal subjects, the diurnal variation in the amount and concentration of the urine excreted is chiefly accomplished by greater or lesser reabsorption in the tubules, and the total amount of glomerular filtrate is altered but little.

Discussion. Experimental work on rats and rabbits with one kidney removed shows that compensatory changes may take place in the remaining kidney.[2,3,4,5] These changes often consist of an early opening up of a greater proportion than usual of the glomeruli. Later the renal tissue may increase, owing chiefly to an enlargement of the glomeruli and tubules. Whether or not new glomeruli are formed is disputed.

Hinman[2] has reviewed this subject exhaustively with particular regard to the renal hypertrophy and hyperplasia which may take place in one kidney following damage to the other. Addis, Myers and Oliver[6] found that in the rabbit the urea clearance values were only about 66 per cent of normal 3 to 4 months after nephrectomy, which corresponded closely to the relative weight of the hypertrophied remaining kidney. In dogs, following nephrectomy, there is an immediate depression of function, but the urea excretion is normal in about 11 days.[2] Foster[7] studied 9 patients within 3 weeks after nephrectomy and found the phenolsulphonphthalein excretion normal and the kidney's concentrating ability little if any impaired. In these patients the Addis urea test showed values ranging from 19 to 36, whereas 50.4 is the theoretical normal. Seven of the 9 patients were suffering from renal tuberculosis.

Our results show that following unilateral nephrectomy there may or may not be detectable impairment of renal function.

Immediately following the removal of the kidney the renal reserve in the remaining one is brought into play. In our Cases 1 and 2 it is probable that the increase in function was accomplished partly by greater filtration through the individual glomeruli. Since the tubular reabsorption of fluid was diminished, as indicated by the concentration tests, and since there was no evidence of damage to the tubular cells which could explain this decreased reabsorption, it is probable that it was due to an increased volume of filtrate flowing down each tubule.

The examinations in Cases 1 and 2 carried out 4 to 5 months postoperatively showed no change in function, suggesting that in these particular cases there was little or no actual structural hypertrophy of renal tissue within this period of time. However, subsequent to unilateral kidney removal certain compensatory changes may conceivably take place. Groups 2, 3 and 4 illustrate these changes.

1. There may be functional or structural compensatory changes in both glomeruli and tubules producing a normal renal function. Cases 3 and 4 may be of this type.

2. There may be compensatory changes in the glomeruli, but the tubular compensation is relatively less. Consequently, the total glomerular filtrate is normal in amount but the reabsorbing ability of the tubules is inadequate to provide maximal concentration (Cases 5, 6 and 7).

3. The glomeruli may not undergo compensatory changes and the glomerular filtrate may remain diminished below normal. Under these conditions the tubules can reabsorb water to a high degree and, moreover, they are apparently able to readjust themselves qualitatively so that less urea than normal diffuses back through their walls into the blood. Therefore, although the values found for the creatinin clearance (*i. e.*, filtrate) are somewhat low, the urea clearance values are normal. Cases 8 and 9 belong in this group.

This study also furnishes some information as to the sensitivity of the functional tests employed. In Cases 1 and 2 approximately 30 per cent of the total amount of functioning kidney tissue had been recently removed at operation. Both the creatinin and urea clearance tests showed a reduction of this order of magnitude from the average normal. It would seem not improbable, therefore, that the creatinin clearance test actually gives an absolute and the urea clearance a relative index of glomerular filtration. The values obtained by the urea clearance procedure, however, may be influenced by changes, compensatory or otherwise, which may occur in the tubules. This, however, does not impair the clinical value of the test.

The concentration test does not measure the total amount of functioning tubular tissue, but rather the conditions under which the individual tubules operate. That is, on the one hand, if the quantity or velocity of fluid passing down a normal tubule is increased, it will be unable to concentrate to the usual degree; on the other hand, if the actual tubular structure is altered by disease, an individual tubule may prove incapable of concentrating a normal or even diminished amount of glomerular filtrate. Therefore, an accurate evaluation of the nature of any disturbance in tubular function detected by a concentration test, can be properly attained only by correlation with an estimate of the amount of glomerular filtration.

This study indicates that the renal function of persons with one kidney is completely adequate for their daily needs. The only hazard to such individuals is in the development of complicating disease in the remaining kidney.

Summary and Conclusions. 1. The renal function of 12 patients who had undergone unilateral nephrectomy was studied by urea and creatinin clearance, concentration and phenolsulphonphthalein tests. Nine of the patients were quite healthy, 2 had pyonephrosis of the remaining kidney and 1 had hypertension.

2. The 2 cases which were studied immediately after operation

showed diminished values for the clearance and concentration tests. The tests on 7 other uncomplicated cases were normal in 2, and one or more of the tests were slightly abnormal in 5. The 3 patients with complications had marked impairment of renal function.

3. In the absence of complications, the renal function of persons with one kidney is not only adequate, but possesses a reserve capacity as well.

4. The observations confirm the value of urea and creatinin clearance tests in detecting early and quantitative reductions in glomerular function and of the concentration test as a measure of tubular reabsorptive power.

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NOTES ON THE NATURE OF THE SPLENIC CHARACTERS IN BANTI'S SPLENOHEPATIC ANEMIA AND A METHOD FOR SCORING THEM.

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The following notes will attempt to assist in the verbal delineation of the spleen in the conditions known as Banti's disease and splenic anemia. The work is a part of the studies attempting to give score values to the diseases of this organ, these notes being particularly devoted to the study of a special group.

The evaluation of changes in the spleen, a sort of scoring system, grew from a request by a surgeon to give figures comparable to those in the method used in the tabulation of tumors, while the part concerning the splenic anemias grew from a remark by an internist that the pathologist could not help in a clinical diagnosis by examination of an excised spleen. Attempts at scoring have met with the difficulty that was foreseen, that of giving a numerical value to a qualitative change. The difficulty of distinguishing between the splenic anemias on the basis of splenic pathology is that there is no clear definition of the clinical terms "splenic anemia" and "Banti's disease."

Studies of this subject fall into the following headings: (1) A description of the tissues from presumably normal and from pathologic organs and the numerical evaluations to be put upon them; this is the basis of a scoring system. (2) The identity of the clinicopathologic states called splenic anemia and Banti's disease. (3) The character of the spleen in the two. (4) The distinctions, if any.

Technique of Scoring. The scoring of the spleens was started by preparing a chart to cover every possible alteration in the gross and microscopic anatomy of the organ. This has suffered many modifications and reductions, until finally it was decided that scoring of the gross anatomy was not at all profitable. Numerical evaluation has not led to a final scheme of scoring in figures approaching in definiteness that used for epidermoid carcinoma, which in itself is useful in only a broad and relative manner and by those familiar with it. None the less, a helpful scheme for the micro-anatomy was produced by reducing to the minimum the characters (Table 1) that had to be evaluated, which were found to be 13 in all. Their nature is discussed in the following paragraphs as a basis for these descriptions and enumerations.

TABLE 1.—EXAMPLES OF THE SCORING OF SPLEENS ACCORDING TO THE ARBITRARY MATHEMATICAL SYSTEM AND THE OBSERVATIONS JUST MADE.

	Theoretically normal.	Actual reading normal age 19.	Actual reading normal age 22.	Reading of most complete case of proven Banti's disease.	Reading of almost typical case of splenic anemia, clinically. Traces of case lost.	Score of purpura hemorrhagica.
Follicles	2	2	3	1	3	3
Germ centers	2	1	1	1	2	3
Pulp	2	2	2	1	1	2
Sinuses	2	2	3	3	3	3
Sinus endothelium	2	2	2	3	2	2
Bloodvessels	2	2	2	3	2	2
Bloodvessel wall disease	2	2	3	3	2	2
Fibrous tissue	2	2	2	3	2	2
Reticulo-endothelial cells	2	1	2	3	2	3
Blood	2	2	2	1	3	2
Pigment	2	2	1	3	2	2
Neutrophils	2	2	2	3	2	2
Eosinophils	2	2	2	2	1	1
Total	26	24	27	30	27	29

Two organs of presumably normal character were fortunately obtained, one from an executed man and one from an accidental death; the men were 22 and 19 years of age, respectively. The characters were given a numerical normal value of 2. If they were reduced in number, smaller in size, they were estimated as 1, whereas, if they were increased, hypertrophic or hyperplastic, they were scored as 3. Allowance in a side chart was made for adventitious changes such as the appearance of myeloid cells, amyloid, abscess, tumors, tubercles and infarcts. These were not scored because they would not be present in any normal spleen.

Follicles. The normal follicle is assumed to be a fairly solid collection of lymphoid cells either as a true Malpighian body or as a periarterial spindle. In youth up to 10 years there may be a recognizable "germ center" in a large percentage of follicles. After youth they become progressively fewer and one or two per ordinary section would be within normal limits; if there were none at all they would be registered as reduced.

The normal *follicles* vary from 60 to 100 per sq. cm. of the average microscopic specimen taken just within the subcapsular area. The measurement of their width is so variable that it cannot be quoted even within wide limits. The number of the follicles in enlarged spleens is usually reduced. In none of the spleens of any kind in all this study has there been any evidence of an increase in the number. The number of follicles per sq. cm. in cases diagnosed as Banti's disease has ranged from 9 to 33. The gross bulk of these spleens has been from 2 to 2½ times the bulk of normal spleens. The bulk of the spleen has been determined by the amount of water displaced. It would, therefore, appear that the reduction of follicles is not due to their disappearance but to their inactivity and their compression by the increased interlying organic mass. Two of the spleens, coming from cases not diagnosed as Banti's disease, had, respectively, 34 and 47 follicles per sq. cm. of a pathologic section and their organic bulk was about twice the normal bulk; the bulk of these two organs was less than that of the spleens from cases satisfactorily diagnosed as Banti's disease. It would appear that those cases that are probably different from the acceptable Banti anemia may have less reduction in the number of follicles as well as less atrophy of the individuals.

The small *splenic lymphocytes* are usually arranged in cords but this systematic and conventional construction is not traceable in all pathologic spleens. These cells must be judged by their apparent abundance or paucity in a given specimen by comparison with an acceptably normal one. In the hemorrhagic purpuras, sometimes in the primary anemias, and in most of the infectious processes, there is an abundance of splenic cells with considerable cytoplasm and a relatively loose nucleus that are to be considered as young or swollen small lymphocytes. Cells corresponding to the youngest or lymphoblast type are only recognizable by special cytologic techniques. Hyperplasia of these elements is to be looked for only in leukemias and some infectious diseases.

Sinuses. Under normal conditions the sinuses are usually traceable but are best seen in early hyperemia, both active and passive. One must know in judging a given spleen if it has been incised or perfused. The sinus reticulum is detectable with difficulty and for its demonstration the organ cannot be pressed but should be fixed with the greatest care, whereupon special stains by the silver methods will reveal the delicate filamentous tracery. It is practically absent in chronic splenomegaly, fibrosis beside the sinus overshadowing it in density. Sinus endothelium is flat and obscure in the normal organs but it is prominent in all chronic conditions and in the majority of acute ones also. In the chronic cases it often seems heaped up. The cells comparable to it seem to occur in groups beside the sinuses and sometimes beside the trabeculæ. On one occasion a perfect mantle of endothelium was seen around an arteriole, the arrangement suggesting that of endothelioma; this was not in a case of tumor or Gaucher's disease but in a hemolytic anemia. In the early cases of the Banti type there is a moderate prominence of these cells but in the late cases they are not conspicuous.

Bloodvessels and *their walls* in the normal spleen are not particularly prominent but show considerable variation in different parts of the same organ. They should only be readily discernible near trabeculæ and in follicles. The walls of vessels are, after adolescence, frequently abnormal;

about one-fifth of the vessels in the two supposedly normal spleens studied showed hyalin change of the media, occasional swelling of the endothelium and unusually wide adventitia.

Fibrous tissue in the normal spleen is best understood by the use of a stain like phosphotungstic acid-hematoxylin, the special ones like silver impregnation giving too great a contrast and prominence to the supporting framework. By a good stain it is evident that the fibers are coarser and more numerous than has been usually described. There are two places in which the normal supporting tissue is best examined—around the follicles and just outside the sinuses.

The lower degrees of fibrous tissue increase are difficult to decide upon; more advanced grades are relatively easy. Apparent or relative decrease in fibrous tissue is perceptible in the acute "splenic tumors" such as occur in septicemia and typhoid and in the chronic swellings of the purpuric and hemolytic types. It is in both instances almost certainly relative, there being no reason to assume that true destruction occurs.

Reticulo-endothelial cells are usually plainly visible in the two forms that may be recognized for the spleen—the large mononuclear lying in a lacuna of the pulp and the medium sized mononuclear lying between the sinuses and lymphoid groups. Their increase is perceptible, and largely confined to the medium sized mononuclears, there being increase of giant mononuclears only in the lipoidic spleens. A decrease in the mononuclears is probably relative and only to be expected when their place is taken by blood, fibrous tissue and lymphocytes. Sometimes these cells are distinctly phagocytic, but in the absence of marked pigmentation, phagocytosis is not a prominent feature of splenic pathology; the malarial and hemolytic anemias are exceptions.

The presence of *blood* within vessels and sinuses and diffusely within the splenic tissue is readily perceived, but its amount depends upon the method of the removal of the spleen and its treatment afterward. In the more acute cases of the hepatosplenic anemias the blood is found uncoagulated and agglutinated; in some of the later cases both of these features may be found.

Pigment under normal conditions is sparse in the spleen and yet, in the two probably normal spleens studied, several small groups were found lying free and one large group was found in a giant mononuclear.

Neutrophils scattered singly throughout the tissue are much more common than is generally supposed; this is also true of the eosinophils. Under conditions of acute infection, hemolytic anemias, Hodgkin's disease, tuberculosis and the like, both of these types may be found increased. In 18 cases of the Banti type that we have examined especially for this cell, they have exceeded normal 4 times. Eosinophils are, however, definitely less readily found than are the neutrophils, but occasionally they may be quite prominent. They seem to be more common in the younger cases than in the older ones of chronic splenomegaly, and are very conspicuous on account of their redness.

Splenic anemia may be defined, according to the writings of Osler (1902), Stengel (1904) and Rolleston (1914), as a chronic anemia with splenomegaly (which is often the first change), of unknown cause, with a blood picture with a low color index, a reduction of red cells possibly hemolytic in origin, leukopenia or normal white count, moderate reduction of thrombocytes, no lymph gland enlargement, liability to gastro-intestinal hemorrhages and with an illness naively stated by Rolleston as "prolonged with a tendency to spontaneous cure and with splenectomy curative, if successful."

Banti's disease is like this, but passes into a stage in which cirrhosis of the liver is the prominent pathologic feature and which is combined with jaundice, ascites, further anemia and fatal end. According to Rolleston, Banti's disease occurs more in females and below full middle age; he suggests that the reverse is true in splenic anemia.

Briefly then, the distinction from a clinical standpoint is that in splenic anemia there is no hepatic disease, whereas when cirrhosis and ascites appear it should be called Banti's disease. MacCarty in his analysis states, "For practical purposes the two diseases are usually considered as one."

It might be profitable to devote a few lines to indicate how these words came into use and make mention of a recent discussion on the subject. Stengel credits the origin of the term splenic anemia to W. Griesinger in the middle of the 19th century, but adds that Banti emphasized the term in 1884. Banti himself states that Gretzel (a pupil of Griesinger) in 1866 first made use of the name.

The Italian author described a disease of three stages, insidious and of long duration, many years indeed, consisting of anemia and enlarged spleen, a quiescent period of variable length and a terminal stage of hepatic cirrhosis and ascites. He recognized the similarity of this disease and splenic anemia but insisted that they were different because of the duration, course and hepatic change. Senator, 1901, noted that to the symptom complex described by Banti, gastro-intestinal hemorrhages and local escape of blood might be added. He thought that hepatic cirrhosis need not cause the ascites which could be due to venous obstruction by the large spleen.

Disease of the walls of the splenic artery and vein have been mentioned several times in the literature and thought to be the cause of the splenohepatic disease. Certain other diseases, such as Gaucher's disease and tuberculosis of the spleen, were formerly confused with the conditions under discussion.

Rolleston, commenting on these diseases, makes the point that the stages need not be so protracted as Banti would have it and may indeed so run together that no sharp limits can be detected. He states that there are certainly cases corresponding to the description of Banti but that they appear to be more in the ward than on the autopsy table.

At the meeting of the Association of American Physicians, May, 1932, a discussion took place under the stimulation of a report by Howard and Mills, whose work credited the existence of a clinicopathologic state that corresponds to Banti's disease, yet over half of their cases failed to show hepatic changes. Dr. Howard thinks that only a limited number of cases should rightly be called Banti's disease, but that such undoubtedly exist.

Possibly some of the following considerations will help to decide whether these two terms are justifiable. The condition has not much improved since the very pertinent words of Stengel, 1904,

when he states: "It would be hopeless in the present state of knowledge to attempt a classification of all of the cases that have been reported. On the other hand, it is very evident that there are very different sorts of cases that have more or less superficial resemblance, and I cannot share the view that all are probably instances of one disease in different stages."

Judging from 13 fresh spleens that have been examined grossly and in which clinical diagnoses were acceptable, the features were so nearly constant without regard to diagnosis that they may be described together. Whether or not there are several diseases represented, the gross appearance of the organ does not help to solve the matter. To these have been added the records of 10 other cases and all 23 have been studied microscopically.

The Spleen. It weighs from 600 to 1600 gm. The general shape is preserved, the notch being usually perceptible. The general splenic outline falls within normal variations; the capsule is slightly thickened, smooth, regular, translucent. There may be patches of local chronic perisplenitis, which are best ascribed to reaction to local trauma or to inflammation in the vicinity; there is no reason to believe that perisplenitis would arise from endosplenitis. The cross section is usually dark brown, firm, rather homogeneous in appearance with a perceptible increase in delicate red-gray strands that correspond to a multiplicity of fine trabeculæ. Faint red-gray dots may suggest the Malpighian bodies but a prominence of such markings has not been recorded.

It has been one of the outstanding pathologic and etiologic features of the pathologic anatomy of the spleen and liver in these conditions to emphasize the existence or possibility of sclerosis of the splenic vein and of the gastro-splenic artery. In 1 case, of the series here discussed, there were found endophlebitis and obliterative endarteritis between the liver and spleen, and in 1 case a sclerosing and calcifying phlebitis. The condition of the splenic vein should be noted with greater exactness by both surgeons and pathologists.

The microanatomy of the spleen in the cases of the present study is now taken up in order of the features that we have found important.

The capsule is slightly thickened, and beneath it there is no loose space that could pass for a marginal sinus, the pulp tissue growing up directly to the fibrous coat.

The follicles are diminished in number and size. The "germ centers" are for the most part somewhat below normal limits of size and number, although there are many instances in which they may be plainly seen. Where they are seen there is a hyalin change in the interstitial fibers, or the entire central zone of the follicle may be a hyalin mass with a cell or two and usually without recognizable bloodvessels. This hyalin mass may at times contain many silver-staining fibrils.

It has already been emphasized that the number and size of the follicles should be estimated in terms of the size of the whole spleen. This relative value assists very materially in estimating their increase or decrease—an item again mentioned in discussing two spleens that vary in microscopy from the Banti picture.

The pulp is usually poor in small lymphocytes and, with rare exceptions, never contains what would be called an excess thereof.

The sinuses are for the most part dilated. The sinus endothelium is usually inconspicuous. It may seem atrophic and there is rarely, if ever, a desquamation of endotheliocytes. Care must be taken in interpreting this, because in many studies spleens are perfused while many others are opened and allowed to drain and collapse. When the organ is removed by operation the hemostats or clamps should be allowed to remain on the vessels of the stalk until the pathologist has opportunity to perfuse the spleen or cut it immediately before it is put into fixative. About one-third of our specimens were perfused. The irregularity of the chance to carry out this technique has made it almost an impossibility to compare organs removed during early stages *versus* those from cases of longer duration.

The bloodvessels are within normal limits of number. The arterioles of follicular centers, of the edge of trabeculæ and the occasional one in the pulp, show slightly more disease in the wall than they would in a presumably normal spleen of comparable age; this is true irrespective of the duration of the disease.

The veins of trabeculæ are usually distended. There is often a hydropic change in the media and on two occasions there were early calcium deposits. Marked pathologic change in these veins is, however, not an outstanding feature.

Fibrous tissue is everywhere increased. In the cases in which the spleen has been removed less than 1 year from the inception of symptoms, the fibrous tissue increase is almost as easily recognized as in cases existing much longer than this. Occasionally a deeply stained band, shown by Van Gieson or silver methods, may completely surround a follicle. The perivascular fibers are prominent. The trabeculæ seem to spread out as numerous delicate, yet intricately wound and mixed silver-staining fibers; some of the strands running through the pulp may be massed and hyalin.

Reticulo-endothelial cells appear to take the usual two forms. The large single mononuclear giant cell is not increased; the moderate sized mononuclear, resembling an endotheliocyte, is definitely increased. The endotheliocyte is plainest in spleens that have been removed about 1 year after inception. They lie along the sinuses, sometimes in veins and occasionally in a row along the connective tissue strands. It does not seem possible that their number contributes very greatly to the increased size of the organ.

The amount of blood in the organ, as judged by the microscopic

appearance, is quite variable. It gives a slightly lower score value in spleens removed within 3 full years since the first symptom, and more in organs removed in later years. This observation is not in accord with those on specimens studied by the writer some years ago, coming from supposed Banti's disease of less than a year's duration, that were found to contain much more blood, while another case of long standing was quite poor in free blood. Aschoff and McCallum think that the earlier stage is accompanied by excessive bloodiness. However, not all cases progress at the same rate, and not all spleens have been handled for examination in the same manner.

Pigment is slightly increased and varies directly with the amount of blood perceptible in the sections.

Neutrophils, eosinophils and plasma cells appear to be of no significance. Other recognizable marrow elements are not recorded.

There are 2 cases in the 23 specimens in which the follicles stand out as different from the others and in several ways there are slight variations from the picture just given. These 2 cases deserve a little attention.

The follicles in these cases were all larger than the average of the 2 presumably normal organs and of 34 routine spleens from autopsy material. In these 2 the "germ centers" were apparently more prominent. In both cases the bloodvessels were more numerous. The reticulo-endothelial cells were less conspicuous, the blood within normal limits, the pigment perhaps slightly increased. These cases, respectively 4 and 22 years old, both had their spleens removed after at least 1 year of illness (one 5, the other unknown). The distinction of these two spleens from the others is more readily apparent to the eye than from the written description. They have been diagnosed as splenic anemia, an apparently justifiable distinction in at least one of them, since there was neither jaundice nor ascites, and 3 years have passed after splenectomy without the appearance of ascites.

The liver in the 23 cases has been changed clinically in 10 of 16 instances where it is mentioned, and actually changed, as seen at operation or autopsy, in 7 out of 14 in which it is mentioned. Jaundice was present in 3 out of 14 cases, of which the history records dependable observations. Ascites was present in 6 out of 20 cases and corresponded with definitely known change of the liver 4 times out of the 6. Of the 23 cases, 6 died following splenectomy, 8 are reported living 3 to 8 years and all are invalided. Six of these 8 are recorded as having had postoperation hemorrhages.

Discussion. A distinction of the types of spleens and a clear separation of all these cases into splenic anemia on one hand and Banti's disease on the other seems at present very difficult. The clinical evidence at hand supports strongly the thought that there is a probability of liver damage in most cases of chronic spleno-

megaly. Only 2 of 14 traceable cases seem to have passed 2 years without clinical or definite pathologic information that the liver was involved. The evidence would support the idea that there is a condition of Banti's disease, the early stages of which are splenomegaly with anemia. The late stages are chiefly hepatic with jaundice and ascites. The name Banti's splenohepatic anemia is suggested. Those that do not fall into this group, ably covered by Stengel,[4] remain yet to be classified and the term splenic anemia would better be restricted to description and discussion.

The spleen of Banti's splenohepatic anemia can be described as an enlarged organ, without characteristic capsular change, with reduction in the size and relative number of follicles, fibrosis of follicular centers, of pulp and of trabecular lines, a prominence of mononuclears, a relative atrophy of the pulp, and a variation of blood and pigment depending upon the duration of the enlargement. It is distinct from the enlargement due to primary hepatic cirrhosis which has marked congestion, pigmentation, prominence of lymphoid structures and limited fibrosis. It is distinct from the hemorrhagic purpuras and anemias which have much blood and pigment, a prominence of endothelial cells and phagocytes, and a relative paucity of silver-staining fibers. It is distinct from malarial spleens because the latter show pigmentation, a fine fibrosis, diffuse lymphoid hyperplasia with much phagocytosis. It differs from the syphilitic and tuberculous spleens by the absence of distinct inflammatory foci. With these one finds a combination of marked sinus catarrh, plasma cells and eosinophils; masses of endotheliocytes may be present in these spleens. It is separated from Hodgkin's disease of the acute type by the presence in the latter of large zones of endotheliocytes, giant cells, eosinophils and polymorphonuclears, and from the chronic type with less ease because of the irregular fibrosis of this form.

It would seem from this survey that a strict scoring of the splenic characters will not lead to a numerical value that can be definitely identified with these specific clinical or pathologic entities. By familiarity with this method, or one like it, it may be possible to obtain distinct leads as to the part of the organ that is giving the most definite reaction.

The characters discovered do not permit a sharp separation of the spleens that come from cases called Banti's disease and those called splenic anemia. Many chronic splenic anemias are associated with hepatic disease comparable to that described by Banti. The clinical terms are not used with critical care. It cannot be stated that any considerable number of the cases with splenomegaly and anemia, in which splenectomy was done, may not have terminated with hepatic disease. These studies include one complete record of Banti's disease diagnosed before splenectomy, when there was nothing to suggest hepatic disease by observation at laparotomy,

that died from pneumonia 2 years later and showed a cirrhosis and ascites.

Therefore, it seems acceptable to use the term "splenohepatic anemia" or "Banti's disease" and to omit the clinical diagnosis of splenic anemia, employing instead "anemia with splenomegaly." There may be cases in the melange of the obscure anemias that have simply enlargement of the spleen, anemia and gastro-intestinal congestion that will not go on to hepatic pathology. They are probably rare and further study may identify them.

The characters of the spleen in Banti's disease will help to make the clinical diagnosis and are to be summed up as diminution in the size and relative number of follicles per square area; an increase of fibrosis around follicles, along sinuses and in the neighborhood of trabeculæ, and a prominence of many fine trabeculæ; a hyalin accumulation in the center of follicles, a prominence but no great exaggeration of large mononuclears, and a slight increase of pigment.

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DETERMINATION OF NON-PATERNITY BY MEANS OF BLOOD GROUPS.

With Special Reference to the Agglutinogens M and N of Landsteiner and Levine.

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In our country the possible application of blood grouping in medicolegal cases for the determination of non-paternity has not received the recognition that it has received in many European countries. So reliable is the application of blood grouping for this purpose, that in 1929 Schiff[1] succeeded in collecting 5584 cases in which blood groups had been so applied in Germany, Austria, Denmark, Sweden and Switzerland. Since 1929 this method has also been adopted in Russia, Norway, Japan, the Netherlands, Italy, and Great Britain.

That human bloods can be subdivided into definite groups, because of the ability of the serum of one normal individual to agglutinate the red blood cells of certain other human beings, was first recognized by Landsteiner in 1900.[2] Landsteiner explained this phenomenon by postulating the existence of two isoagglutinogens, A and B, in the red blood cells, and of two isoagglutinins, α and β, in the blood serum, such that α is specific for A, and β is specific for B.[3] In Table 1 is shown the difference in composition of the 4 Landsteiner blood groups, together with the old numberings of Moss and Jansky, and the international nomenclature officially recognized by the Health Committee of the League of Nations. The old nomenclatures, no longer used in scientific publications, are only given here because they are still being used in some of our hospitals. The existence of two systems of numbering has resulted in confusion on many occasions, and has also been responsible for several transfusion accidents. Since the international nomenclature depends upon the agglutinogen content of the red blood cells, it can cause no confusion.

TABLE 1.—CLASSIFICATION AND COMPOSITION OF THE LANDSTEINER BLOOD GROUPS.

Jansky.	Moss.	International.	Cells (agglutinogen).	Serum (agglutinin).
I	IV	O	—	α and β
II	II	A	A	β
III	III	B	B	α
IV	I	AB	A and B	—

In 1908, Epstein and Ottenberg presented the first data on the heredity of blood groups.[4] In 1910, von Dungern and Hirschfeld[5] showed that the agglutinogens A and B are inherited as Mendelian dominants; and in 1924, Bernstein[6] demonstrated that the heredity of the agglutinogens A and B depends upon three allelomorphic genes, A, B and R, where A and B are dominant, and R is recessive. Therefore, the 4 blood groups may be subdivided into genotypes as follows: Group O, genotype RR; Group A, genotypes AA and AR; Group B, genotypes BB and BR; and Group AB, genotype AB. The heredity of the Landsteiner blood groups, according to the Bernstein theory, is shown in Table 2.

TABLE 2.—HEREDITY OF THE LANDSTEINER BLOOD GROUPS.

Groups of parents.	Groups of children possible.	Groups of children not possible.
O × O	O	A, B, AB
O × A	O, A	B, AB
O × B	O, B	A, AB
A × A	O, A	B, AB
A × B	O, A, B, AB	
B × B	O, B	A, AB
O × AB	A, B	O, AB
A × AB	A, B, AB	O
B × AB	A, B, AB	O
AB × AB	A, B, AB	O

How the blood groups can be applied in an actual paternity case is illustrated in the following two hypothetical examples: A man charged with the paternity of a child denies ever having had intercourse with the plaintiff, so the blood groups of man, woman and child are determined. The man is found to belong to Group A, the woman to Group A, and the child to Group B (see mating 4 of Table 2). Since the mother does not possess agglutinogen B, but the child does, this agglutinogen must have come from the father, who could therefore only belong to Group B or Group AB. The blood groups in this case, therefore, have furnished absolute proof of the man's innocence. Let us suppose, on the other hand, that in another similar case the blood groups were as follows: man, Group B; woman, Group A; and child, Group AB. As may be seen from Table 2 (see mating 5), such a combination of groups is entirely possible. This, however, is no proof that the man charged with paternity is the true father; for in a population such as that present in this country, about 15 per cent of all individuals belong to Group B. The man in question is no more proved to be the father than is any other man belonging to the same group. Blood groups, therefore, are of no value as an aid to proving paternity; they can only be used to prove non-paternity.

In not every case where a man is unjustly accused of paternity is it possible to exclude him as a father of the child. Thus, if the putative father and the true father both belong to the same group, no exclusion will be possible. It has been calculated that the average chances of proving non-paternity by means of the Landsteiner blood groups are approximately 1 in 6.[7,8]

The chances of proving non-paternity have been doubled by the discovery by Landsteiner and Levine of several additional agglutinogens in human red blood cells.[9] Two of these, termed M and N, respectively, were studied in great detail, and Landsteiner and Levine demonstrated that they are inherited as Mendelian dominants.[10] According to their theory, the heredity of these agglutinogens depends upon a single pair of allelomorphic genes, M and N. There are therefore only three genotypes possible: MM, MN, and NN; corresponding to the three phenotypes: M+N− (blood possessing agglutinogen M, but lacking agglutinogen N), M+N+ (blood possessing both agglutinogens, M and N), and M−N+ (blood possessing only agglutinogen N). According to the theory, therefore, bloods of type M−N− (lacking both agglutinogens) are impossible. As a matter of fact, although almost 20,000 specimens of blood have been examined to date by Landsteiner and Levine, Schiff,[11,12] Wiener, *et al.*,[13,14,15] Thomsen,[16] and Clausen,[17] not a single blood lacking both agglutinogens has been found to date. The present author has personally examined more than 3000 specimens of blood without finding a single exception to this law. This, certainly, is impressive confirmatory evidence of the theory of Landsteiner and Levine.

The heredity of the agglutinogens M and N is very easily derived from the theory, as shown in Tables 3 and 4. Thus, in the M+N− × M+N− mating, the genotype of both parents is MM. The gametes (sperm and ova) each contain the single gene M, so that all the zygotes must be of genotype MM. All the children of such a mating must therefore be of type M+N−. Similarly, in the M+N− × M+N+ mating, the genotypes of the parents are MM and MN, respectively. The former parent can only produce gametes containing gene M, the latter parent produces gametes with gene M and gametes with gene N in equal numbers. Half of the zygotes must therefore be of genotype MM and half of genotype MN, corresponding to the phenotypes M+N− and M+N+, respectively. The other four matings in Table 3 were worked out in a similar manner.

TABLE. 3.—HEREDITY OF AGGLUTINOGENS M AND N.

Cross.	Per cent children of types.		
	M+N+	M+N−	M−N+
M+N+ × M+N+	50	25	25
M+N+ × M−N+	50	0	50
M+N+ × M+N−	50	50	0
M+N− × M−N+	100	0	0
M+N− × M+N−	0	100	0
M−N+ × M−N+	0	0	100

TABLE 4.—MEDICOLEGAL APPLICATION OF THE AGGLUTINOGENS M AND N.

Types of parents.	Types of children possible.	Types of children not possible.
M+N+ × M+N+	M+N+, M+N−, M−N+	
M+N+ × M−N+	M+N+, M−N+	M+N−
M+N+ × M+N−	M+N+, M+N−	M−N+
M+N− × M−N+	M+N+	M+N−, M−N+
M+N− × M+N−	M+N−	M+N+, M−N+
M−N+ × M−N+	M−N+	M+N+, M+N−

Technique. The technique of testing for the agglutinogens M and N is much more complicated than the technique of testing for A and B. There are no natural agglutinins for M and N; the testing sera are obtained by immunizing rabbits. To produce anti-M serum, blood of type M+N− should be used; to produce anti-N serum, blood of type M−N+ is used. The blood selected should also belong to Group O, so that no agglutinins are formed against A and B. The technique I have found most effective is to alternate courses of daily intravenous injections with long rest periods. If 12 rabbits are to be immunized, 25 cc. of blood will suffice for one course. The blood should be divided among 7 or more tubes (for a course of 7 days or longer), containing the following solutions, recommended by Rous and Turner[18] for preserving blood: 5.4 per cent glucose (5 parts); 3.8 per cent sodium citrate (2 parts); whole blood (3 parts).

The solutions must be sterile, and the blood must be collected under sterile precautions. When stored in the ice box in this manner, blood may be kept for several weeks. Before injecting the blood into the rabbits, the contents of each tube should be washed with sterile saline and then diluted up to a convenient volume. The washed blood is then divided equally among the 12 rabbits. All the injections of the first course are given intravenously. The first injection of each of the subsequent courses is given

intraperitoneally (to avoid anaphylaxis); all other injections are given intravenously. The rest periods between courses should be about 7 to 10 days. The rabbits are bled and the sera examined for their agglutinin content 1 week after the last injection. After 3 or 4 courses of injections, most rabbits will produce good anti-N sera. It is much more difficult to produce anti-M sera, however. We finally succeeded in producing a very potent anti-M serum, by giving 2 rabbits which had had several courses of injections, followed by a rest period of *several months*, 1 additional course of injections. When preparing these sera it is wise to start with a large series of rabbits, since because of the protracted nature of the immunization (particularly for M), most of the rabbits will die before the experiment is completed.

To test the sera a few cubic centimeters of blood are collected from an ear vein and then allowed to clot. The serum is separated off by centrifuging, and then inactivated by heating to 56° C. for half an hour. This serum not only contains agglutinins against M (if the rabbit was immunized with M+N− blood) or N (if the rabbit was immunized with M−N+ blood), but also species agglutinins acting on all human blood. A potent serum will agglutinate any human blood at a titer of 1 to 3000. To prepare the testing fluid from the serum, the species agglutinin must be removed by absorption. We prepared our anti-M fluid from serum M 905. This serum was diluted 50 times and mixed with half a volume of packed, washed cells of type M−N+. After standing for 30 minutes at room temperature, the mixture was centrifuged at high speed. The supernatant fluid now only contained agglutinins against the factor M. Our N fluid was prepared from the serum of rabbit N 2. This serum was diluted 20 times and absorbed with half volume of packed, washed cells of type M+N− at 37° C. The testing fluids thus prepared were stored in the ice box after the addition of 1 drop of toluol per cubic centimeter of fluid. (The use of this preservative was suggested to us by Dr. Philip Levine. The addition of toluol preserves the testing fluid for more than 6 months. Without toluol, on the other hand, the testing fluid deteriorates rapidly and usually must be discarded after a few weeks.) Before use, the M fluid was further diluted three times (making a final dilution of 1 to 150), and the N fluid two times (a final dilution of 1 to 40).

The blood to be tested is suspended in saline and citrate, washed once and resuspended in normal saline solution to make a 2.5 per cent suspension. One drop of the cell suspension, 2 drops of saline, and 1 drop of testing fluid are mixed in a small test tube, the mixture is then centrifuged for 5 minutes at 1800 r.p.m. After centrifuging, the tubes are replaced in the rack, which is then shaken until the negative control has broken up into an even suspension. (Control bloods of all three types must be included in every experiment.) The reactions for M are always easy to read. There will be occasional difficulty with the N reactions, however, but whenever this occurs the difficulty will resolve itself if several different N fluids are used, and if the tests are repeated a sufficient number of times.

We did not find it necessary to use any preservative for the concentrated immune rabbit serum. After the preliminary tests had been performed, the rabbits which had been found to have potent sera were bled from their marginal ear vein, which was cut after the ear had been previously rubbed with a small amount of xylol. In this manner, as much as 40 cc. of blood could be obtained, and at the same time the rabbit could be kept alive for further experimentation. The blood was allowed to drip into sterile 10 cc. tubes, and after the blood had stood overnight in the ice box the serum was separated by centrifugation. The serum was then transferred to sterile 1 cc. vials by means of sterile pipettes. The vials were hermetically sealed, and the serum was then stored in the ice box. Serum so kept was

found to show no appreciable diminution in titer after two years, provided that there was no contamination. The serum that is to be stored need not be inactivated, since it loses its complement after standing for several days in the ice box.

Though members of our laboratory staff have been repeatedly examined for M and N during the past 3 years, in no case has a change in type been noted.

In Table 5 we have summarized the results obtained up to date on the heredity of the agglutinogens M and N. These data, which include 674 families with 1899 children, present 8 "exceptions" to the theory of Landsteiner and Levine. That these "exceptions" are undoubtedly due to illegitimacy will now be proven.

TABLE 5.—SUMMARY OF ALL DATA ON THE HEREDITY OF THE AGGLUTINOGENS M AND N.

Types of parents.	Types of children. M+N+	M+N−	M−N+	Totals.
M+N+ × M+N+	256	113	93	462
M+N+ × M−N+	218	2	225	445
M+N+ × M+N−	305	260	3	568
M+N− × M−N+	181	0	2	183
M+N− × M+N−	1	157	0	158
M−N+ × M−N+	0	0	83	83
Totals	961	532	406	1899

This table includes:
64 families with 286 children by Landsteiner and Levine.[10]
131 families with 642 children by Wiener and Vaisberg.[13]
72 families with 192 children by Schiff.[12]
290 families with 577 children by Clausen,[17] of which
102 families with 105 children had been previously reported with Thomsen[16] and
117 families with 202 children by Lattes and Garrasi.[20]

For medicolegal purposes the mechanism of heredity of the agglutinogens M and N may be summarized in two laws:

1. The agglutinogens M and N can never appear in the blood of a child unless present in the blood of one or both parents.

2. The combinations M+N− parent with M−N+ child, and M−N+ parent with M+N− child are impossible.

TABLE 6.—SUMMARY OF ALL MOTHER-CHILD COMBINATIONS.

Authors.	Number of mothers.	Number of children.
Landsteiner and Levine (families)	64	286
Wiener and Vaisberg (families)	131	642
Schiff (families)	72	192
Clausen and Thomsen (families)	290	577
Lattes and Garrasi (families)	117	202
Schiff (forensic cases)	..	525
Schiff (newborn)	..	566
Wiener, Rothberg and Fox	461	497
Totals	..	3487

A rigid test of the theory may be made by examining a large series of mothers and their children (to eliminate the possibility of illegitimacy), in order to determine whether or not exceptions to

the second law ever occur. In Table 6, therefore, we have summarized all the mother-child combinations that have been studied thus far. *In this series of 3487 cases, not a single exception to the theory of Landsteiner and Levine was found.* This proves conclusively that it is impossible for an M+N− mother to have an M−N+ child, or *vice versa*. Since the agglutinogens M and N are independent of sex in their heredity, the same statement must also hold for the father. Exceptions to the second law in family studies that implicate the father must therefore be due to illegitimacy.

If we now analyze the 8 "exceptions" in Table 5, we find that 7 of them are "exceptions" to the second law implicating the father, and therefore must be due to illegitimacy, as the authors themselves believed. The eighth case, which was found by Wiener and Vaisberg, is an "exception" to the first law, and is also undoubtedly due to illegitimacy, since such exceptions due to illegitimacy are rather to be expected in studies on a large series of families.

Landsteiner and Levine, and Wiener and Vaisberg also examined their families for the Landsteiner blood groups Landsteiner and Levine found 6 "exceptions" to the heredity of the 4 blood groups due to illegitimacy, whereas Wiener and Vaisberg found only 1, indicating that the morals of the people studied by the former authors were lower. Therefore, the fact that Landsteiner and Levine found 5 of the 8 "exceptions" of Table 5, whereas Wiener and Vaisberg found only 2, corresponds to the expectations.

On the basis of this large series of studies, the medicolegal application of the agglutinogens M and N for the determination of non-paternity is fully justified at present, together with the application of the classic blood groups. By the combined use of all 4 agglutinogens, A, B, M, and N, it is possible to exonerate one-third of all men falsely accused of paternity.

To illustrate the method of application, and also because blood groups have been so little applied in this country for the determination of nonpaternity, I shall quote my experiences in 5 cases:

Case Abstracts. CASE 1 (previously reported[19]).—The question arose in this case whether the husband or another man was the father of a child. The husband was willing to support the child regardless of its paternity, but the wife insisted that she would only live with the child's true father. Dr. A. A. Eggston grouped the bloods of all 4 individuals, but as both men belonged to Group A, no decision could be rendered. He therefore referred the case to me for the application of the agglutinogens M and N. By this method, the lover could be definitely excluded as possible father of the child, since he belonged to type M−N+, whereas the child belonged to type M+N−. Of the two men, therefore, the husband could only have been the true father. The complete results of the blood examinations were:

Blood of:	Group.	Type.
Husband	A	M+N−
Lover	A	M−N+
Wife	B	M+N−
Child	A	M+N−

It is an interesting illustration of human nature that the woman finally left her husband for the lover regardless of the paternity of the child.

CASE 2.—This case was referred to me by Dr. S. H. Polayes, since he could render no decision by means of the classic Landsteiner blood groups. In this case, a man who had relations with his wife before marriage, and who had married her when she told him she was about to give birth to a child, desired a divorce, and as an excuse claimed that the child (at the time 2 years old) was not his. The findings were:

Blood of:	Group.	Type.
Husband	A	M+N−
Wife	A	M+N+
Child	O	M+N+

Since such a combination of groups is entirely possible, it is impossible to determine whether or not the child is legitimate.

CASE 3.—In this case a woman charged a man with the paternity of her child. Although the man admitted having had relations with the woman, he claimed that other men had had relations with her at about the same time. The court ordered blood tests, and the bloods were shipped to me from New Haven. The results were:

Blood of:	Group.	Type.
Putative father	A	M−N+
Mother	O	M+N+
Child	O	M−N+

Here again it is impossible to tell whether or not the man is the father of the child.

This case is important, however, because it illustrates how these tests can be introduced into our courts, provided that the lawyers and judges are progressive enough. The judge who ordered the blood tests for this case (New Haven Court of Common Pleas) stated that this was a new question to him, but if the tests resulted so that the examining physician, upon proper qualification, could state that the defendant could not have been the father, it would be important evidence. The results of the tests in this case left the question open, but upon other evidence, the defendant was adjudged the father of the child.

CASE 4.—This case was referred to me by Dr. W. G. Flickinger. Because he had suspected his wife of infidelity for a period of years, a man desired to have blood tests performed on his wife, his 2-year-old son, and himself. He also had a 14-year-old daughter of whose legitimacy he felt certain. The results were:

Blood of:	Group.	Type.
Husband	A	M+N−
Wife	O	M+N−
Son	O	M+N−

Here again no decision could be rendered.

CASE 5.—After 8 years of married life, during which time she had had frequent intercourse with her husband but had failed to become pregnant, Mrs. X met and fell in love with Mr. Y. Soon thereafter a boy was born, and 3 years later a girl was born. At about this time Mr. X discovered the relations between his wife and Mr. Y. When Mrs. X expressed her desire to leave her husband for Mr. Y, Mr. X threatened to take the case to court, where the custody of the children would most probably be awarded to him. Mrs. X felt that the children were Mr. Y's, and finally persuaded her husband to have blood tests performed. It was found at that time

that the husband, wife, and two children all belonged to group O, and that the lover belonged to Group A, so that no decision was possible. Two months ago a third child was born, a girl; the boy now being 5 years old, and the second child 2 years of age. In order to effect a final solution of their problem, these people came to New York for complete blood tests. The results were as follows:

Blood of:	Group.	Type.
Husband	O	M+N+
Lover	A	M−N+
Wife	O	M+N+
First child	O	M+N+
Second child	O	M+N−
Third child	A	M−N+

It can readily be seen that the lover could not be the father of the second child; and that the husband could not be the father of the third child. No decision is possible concerning the first child. In this case, therefore, our blood tests have succeeded in determining the paternity of 2 out of 3 children; for we have indirectly proved that the second child was the husband's and the third child was the lover's.

CASE 6.—In this case (New Haven Court of Common Pleas) the use of blood-grouping prevented a miscarriage of justice. E. N. charged L. R. with the paternity of her child, and after a preliminary hearing L. R. was held for trial. Although the defendant repeatedly denied his guilt, the weight of public opinion was against him. The attorney for the defendant suggested blood-grouping tests, to which the man, woman and child were subjected. The results of the tests were as follows:

Blood of:	Group.	Type.
Putative father	A	M+N+
Mother	O	M+N+
Child	B	M+N−

Since a Group O mother cannot give rise to a Group B child unless the father belongs to Group B or Group AB, L. R., who belongs to Group A, could not be the father of the child. After conferring with her lawyer, E. N. decided to withdraw her charges, and judgment was rendered for the defendant.

It seems hardly necessary to emphasize the importance of employing the utmost care when applying blood grouping for medicolegal purposes, since errors in technique can only serve to discredit all this work, as well as bringing about grave injustice. When testing for the Landsteiner blood groups, errors are practically impossible if both cells and serum of each blood are examined (see Table 1). Several potent testing sera of each group should be used, and several control bloods of each group should be included in every experiment. The tests should also be performed upon two independent samples of blood.

With respect to the examination of the bloods for the agglutinogens M and N, as we have already pointed out, the technique is somewhat more involved than the technique of typing for the classic blood groups. It is therefore of the utmost importance that the tests in medicolegal cases be performed by experts, *i. e.*, individuals who have done a considerable amount of work in this field and particularly with the agglutinogens M and N.

Summary. The medicolegal application of the Landsteiner blood groups for the determination of non-paternity is urged on the basis of the experiences of European countries during the past 10 years. The application of the agglutinogens M and N of Landsteiner and Levine is also fully justified at present, on the basis of studies on families totaling more than 3000 children. The method of application is illustrated by actual experiences in 6 cases, in 3 of which valuable information was obtained.

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A CHEMICAL PECULIARITY OF PELLAGRA BLOOD (RAPID IODIN DECOLORIZATION).

Preliminary Note.

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In diseases with protean symptoms alterations of the blood are frequent and are often sufficiently well marked to be of diagnostic value. Goldberger[1] has emphasized that many cases of pellagra are overlooked owing to the limitation of their symptoms, in contrast to the manifestations of the well-developed classical case.

To quote, "While there is danger that conditions not pellagrous may be diagnosed as pellagra, there is perhaps greater danger that pellagra will fail of recognition. It is important to keep in mind the possibility of pellagra in cases of 'neurasthenia,' 'melancholia,' 'chronic indigestion with spring exacerbations,' 'dysentery,' 'pernicious anemia,' 'eczema,' 'sunburn,' 'epileptiform seizures,' 'vaginitis,' and obscure abdominal pains suggesting diseases of the ovaries, appendix or gall bladder." A specific change in the blood of known pellagrous cases might, therefore, serve as a criterion for diagnosis of these obscure conditions mentioned above, and for those cases designated by various authors as "pellagra *sine* pellagra."

About 1 year ago the author noticed that the erythrocytes of pellagrous blood caused more rapid decolorization of iodin solutions than other human erythrocytes, whether normal or pathologic. After a series of experiments designed to test this observation, there was developed a technique which promises to be of value as a clinical laboratory test in the diagnosis of pellagra.

Reagents. *Alcohol-ether Mixture.* A mixture of 3 volumes of 95 per cent ethyl alcohol and 4 volumes of ether (commercial or anesthetic ether may be used; chemically pure ether has not been tried).

Iodin Solution. Accurately prepared Lugol's solution (5 per cent iodin in 10 per cent potassium iodid).

Color Standards. Prepare a 3 per cent potassium dichromate solution and from this make the following dilutions: 1 to 5, 1 to 10, 1 to 20, 1 to 40, 1 to 80, 1 to 120, 1 to 240. Place these standards in a series of test tubes of the same internal diameter.

Procedure. *Liquid Petrolatum.* Five cubic centimeters samples of normal or nonpellagrous (control) and of suspected pellagrous venous blood are withdrawn and quickly introduced into 15 cc. centrifuge tubes containing 5 cc. of liquid petrolatum. *The time of collection of each specimen must be recorded.* As each sample is collected, the tube is stoppered and shaken very vigorously until the blood is defibrinated. This may best be accomplished by striking the stoppered end of the tube against the palm of the opposite hand. The specimens are then allowed to stand for 30 to 45 minutes, after which they are again vigorously shaken and centrifuged at 1000 revolutions per minute for 5 minutes. Before the second shaking it is advisable to remove the stoppers momentarily to permit the entrance of air for adequate oxygenation. When the tubes are removed from the centrifuge three distinct layers may be distinguished, namely, an upper layer of fibrin and oil, a middle layer of serum and a lower layer of erythrocytes, leukocytes, etc., which the author shall designate the erythrocytic layer. If any sample has not been properly defibrinated, clots will be present in the lower layer. Such samples should be discarded. One cubic centimeter samples of the erythrocytic layers are now transferred by means of serum pipettes to test tubes of the same diameter as those of the standards. In the removal of these samples from the erythrocytic layer, care must be taken that no oil, fibrin or serum enters the pipette by capillary action as it passes through the two upper layers.

Exactly 1 hour after taking the venous blood specimen, add to the corresponding erythrocytic sample, slowly and without shaking, 5 cc. of the alcohol-ether mixture and stopper the tube tightly. After the alcohol-ether mixture has been added to all samples, let them stand for approxi-

mately 6 hours at room temperature (25° to 30° C.). At the end of this time add in rapid succession to each tube by means of an accurate micro pipette (Folin micro blood pipette or Kahn serologic pipette) a 0.1-cc. portion of the iodin solution. Mix gently and replace the stoppers.

As the mixtures stand there will be noted a gradual diminution of color in each tube, but a greater decolorization in the pellagrous samples. Within 3 hours the extract of pellagrous blood may be completely decolorized while other samples are not. The most constant difference occurs after the tubes have stood about 12 hours. At this time compare the colors of the alcohol-ether extracts with the potassium dichromate standards. The color range of these standards represents that of most samples which have stood 12 hours. Occasionally, however, a pellagrous sample may be completely decolorized, and other samples may be darker than the 1 to 5 standard.

Interpretation. On the basis of cases studied, if the color of the unknown matched that of a standard two shades lighter than the nonpellagrous sample, a mild condition of pellagra was apparently indicated. If it compared with a standard three shades lighter than the normal, a moderately developed condition of pellagra was considered to be present. If the unknown compared with or was lighter than the fourth tube from the nonpellagrous or normal, advanced severe pellagra existed. Often in severe cases of pellagra the extract was completely decolorized at the end of or before 12 hours. Reactions have been designated, according to the above method of interpretation, as mild, moderate, severe and negative.

Conclusions relative to the interpretation of the test have been reached by a study of over 150 hospital and dispensary cases, including a variety of diseases, 50 of which were pellagrous. In this series it was found that definitely diagnosed untreated pellagra cases always gave very positive reactions. No other pathologic condition gave positive reactions except certain cases with varied complaints and obscure diagnoses, and other cases with variable complaints in which pellagra was suspected by the attending physician. Only 5 cases of definitely diagnosed pellagra which gave positive reactions were tested after treatment with yeast. In these cases, after an average of 1 month's treatment with yeast the reaction changed from severe to mild, or negative. Mild reactions were given only by treated cases of definitely diagnosed pellagra, and by some suspected cases which were not definitely diagnosed. Moderate reactions occurred in some of the suspected and undiagnosed cases, in some of the untreated pellagrins, and in some treated cases of pellagra. Severe reactions occurred only in definitely diagnosed, untreated cases of pellagra, in 3 of the suspected pellagra cases, and in some undiagnosed cases in which pellagra was not suspected. The following table gives a summary of conditions tested.

In the suspected and in the undiagnosed cases giving positive reactions, it is my belief that pellagra probably existed. It is in

TABLE 1.—RESULTS OF IODIN DECOLORIZATION TEST.

Diagnosis.	Reaction.	Number of cases.
Definitely diagnosed untreated pellagra	Moderate to severe*	37
Definitely diagnosed treated pellagra, treatment of 2 to 4 months' duration	Negative to mild and moderate reactions	10
Suspected pellagra, not definitely diagnosed	Mild to moderate and severe	6
Active pellagra complicated by other diseases	Severe	3
Undiagnosed cases, pellagra not suspected	Moderate to severe	8
Undiagnosed cases, pellagra not suspected	Negative	4
Addison's disease	Negative	1
Carcinoma of the pancreas	Negative	1
Epidemic encephalitis	Negative	3
Lateral sclerosis	Negative	1
Arterial hypertension	Negative	3
Tuberculosis of the lungs	Negative	5
Syphilis	Negative	5
General paresis	Negative	14
Tabes dorsalis	Negative	1
Dementia precox	Negative	20
Manic-depressive	Negative	4
Granuloma fungoides	Negative	1
Pernicious anemia	Negative	3
Diabetes mellitus	Negative	3
Myocardial disease	Negative	4
Multiple arthritis	Negative	4
Cirrhosis of liver	Negative	1
Acute bronchitis	Negative	2
Carcinoma of rectum	Negative	1
Psychoneuroses	Negative	4
Hyperthyroidism	Negative	2
Psoriasis	Negative	3
Carcinoma of cervix	Negative	1
Carcinoma of stomach	Negative	2
Myelogenous leukemia	Negative	1
Chronic nephritis	Negative	3
Ulcerative colitis	Negative	1
Normal	Negative	6
Total		168

* Reaction after treatment: Five cases observed and all became mild or negative after treatment.

these cases that the test would be especially valuable, and it remains for experience with the test to determine the reliability of the procedure as a criterion of diagnosis.†

† We feel that this preliminary note should be supported by the following statement which did not come to us through the author. Dr. M. R. Everett, Professor of Biochemistry and Pharmacology at the University of Oklahoma, has replied to our letter as follows: "A theoretical consideration of the possible pathology of glutathione metabolism in pellagrins led him to investigate the effects of iodin on the blood of hospital patients. . . . During this work I was almost a constant observer of his technique and to me the results were very striking, pellagrous samples of blood being easily distinguished from all the others, as described in his paper. Often series of samples were numbered and kept as unknowns until the laboratory tests were completed. . . . Dr. Campbell had some of his associates do the technical work of the test to provide a further check. In fact, I am certain that the only possible error in his test would have to be some insidious factor, such as an unknown impurity in his reagents (and, of course, we used various samples of reagents) but, of course, this could only be found by others trying the test. . . . Also Dr. Campbell has had the clinical advice and aid of some of our best clinical associates here. . . ."

Discussion. A detailed discussion of the possible chemical basis of this test must be postponed. Apparently the essential factor is a catalyst, since it is merely the rate of disappearance of the iodin which serves for differentiation. After a sufficient length of time both pellagrous and nonpellagrous extracts are totally decolorized. The very gradual reduction of the iodin in the above procedure points to something other than glutathione as the pertinent reducing factor. This has been substantiated by glutathione determinations in a number of these pellagrous bloods by the method of Woodward and Fry.[2] The glutathione content of these samples was found to be practically the same as that of the normals.

Delaville and Kowarski[3] state that there are two fractions in blood concerned in the reduction of iodin, namely, a rapid one which they believe to be glutathione and a slow fraction, extremely complex, which reduces iodin at a very variable rate. My experiments have shown that the factor responsible for the gradual decolorization of iodin in the alcoholic-ether-erythrocytic mixture was constantly more active in pellagrous samples. Attempts have been made to simplify the procedure of the test described by using oxalated blood, laked corpuscles and whole blood. The results were unsatisfactory and the more complicated procedure described above is the only successful one thus far devised. Further study is in progress.

Conclusions. Pellagrous blood reduces iodin solutions at a constantly greater rate than that of any other blood thus far examined. This phenomenon is made the basis of a test which promises to be of clinical value in the diagnosis of pellagra. Many pathologic conditions have not been examined, and it is possible that further work will disclose that other conditions simulating pellagra may give positive reactions. However, the phenomenon of increased rate of iodin decolorization by the erythrocytes in pellagrous blood may lead to fruitful information bearing on the etiology of pellagra, certain entities of avitaminosis and malnutrition.

NOTE.—Appreciation is extended to administrative and faculty members of the University of Oklahoma School of Medicine and to the Superintendent of the Western Oklahoma State Hospital for the privileges of studying clinical material and for the use of laboratory facilities; also to Dr. M. R. Everett for helpful suggestions.

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MAINTENANCE OF NORMAL BLOOD IN PERNICIOUS ANEMIA BY MEANS OF INTRAMUSCULAR INJECTIONS OF A SOLUTION OF LIVER EXTRACT.*

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In a patient with pernicious anemia the maintenance of an essentially normal condition of the blood and a satisfactory state of health with sufficient liver substance to prevent a relapse is quite as important as that of treating the patient whose blood is in a state of relapse.

This paper deals particularly with the problem of the maintenance care of those patients treated with intramuscular injections of the Solution Liver Extract (Lederle), described in a previous paper.[1] One hundred and one patients have been treated in this manner during a period of 16 months. Six received the extract intravenously at some time during the period of observation. A few of the patients have taken liver or liver extract (fraction G of Cohn) by mouth in place of the injections for varying periods of time, and rarely small amounts of liver substance have been ingested in addition to that received by injection.

Of the 101 patients under discussion 44 received their first parenteral treatment during the time that they were patients in the hospital, and in the majority the blood was in a state of relapse. Fifteen patients who first came under observation with red blood cell counts under 4,000,000 per c.mm. were treated as ambulatory patients. The remaining 42 patients were changed to this form of treatment, having previously been under observation on a regimen of liver or liver extract by mouth. The change in form of therapy was frequently made at the patient's request, or particularly in those patients whose initial blood level was below normal, either because oral treatment was neglected or because a normal blood level was not maintained readily by means of the ingested liver substance. The entire group of patients reported represents a consecutive series and includes many definitely resistant cases.

Method of Treatment. The usual and advised procedure has been to give an initial subcutaneous injection of 0.2 cc. of solution followed in 1 hour by a similar injection of 0.4 cc. If by the end of 1 or 2 hours no evidence of sensitivity (indicated by a chill and rise in temperature) has appeared, a deep intramuscular injection, consisting of 6 cc. of solution

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prepared from 200 gm. of liver, is given. At any time during the next 12 hours a second similar injection is given. At an interval of from 1 to 4 weeks after the initial therapy just described injections are resumed in 3-cc. doses* (prepared from 100 gm. of liver) at weekly intervals until the blood has reached a normal level (5,000,000 or more red blood cells), and then at intervals as indicated by the requirements of the individual patient. An effort has been made to extend the interval between injections only when the level of the blood count and the patient's condition warranted such a change. The presence of symptoms associated with spinal cord damage has been used as an indication for intensive treatment, even though the blood level was high. With such a policy in mind, and counting the number of red blood cells at the time of each intramuscular injection, it has been possible to extend the interval between injections to as long as 6 weeks and still maintain the patient and his blood in a satisfactory condition.

The intramuscular injections are given usually into the gluteal muscles, care being taken to avoid the region of the large bloodvessels and nerves. A 1.5-inch, 21-gauge needle is inserted by means of a quick thrust which renders the procedure essentially painless. The syringe containing the solution of liver extract is fitted to the needle, the plunger withdrawn slightly to be sure that blood cannot be withdrawn, and then the solution is injected slowly. In the event that blood appears in the needle it is to be withdrawn and reinserted.

Iron, usually in the form of capsules of ferric ammonium citrate,† has been given in doses of 3 gm. daily for varying lengths of time at some period during the course of treatment of the majority of the patients. With the rapid production of red blood cells, which occurs during the course of this form of treatment, the available iron reserve is depleted with a resulting apparent "secondary" anemia. This striking relative insufficiency of hemoglobin has occurred rarely in those patients ingesting whole liver, probably because of the iron contained therein, and because of slower regeneration. Generally the use of 100 to 200 gm. of ferric ammonium citrate given in the dose mentioned above is sufficient to bring the hemoglobin content of the cells to normal, and rarely is a second course of treatment necessary. Notable improvement in the patient's general condition, and particularly in the symptoms generally considered to accompany nerve damage, has occurred coincidently with the use of iron.

Treatment During Relapse. Although a discussion of the results of treatment by means of the intramuscular injection of the solution of liver extract during relapse was presented in a previous paper,[1] the results obtained in a much larger group are now available. Satisfactory improvement in the condition of the patient and of the blood has occurred in each instance. There has been, however, considerable variation in the amount of solution used and the time interval necessary in order to bring the red blood cell count and hemoglobin to normal levels. These variations are to be expected and depend upon various circumstances relative to the patient's condition.

* The dose advised refers only to Solution Liver Extract (Lederle) which was used in each instance. Inadequate dosage must be avoided if less concentrated extracts are used.

† Capsules of Ferric Ammonium Citrate (Lederle), 0.5 gm. each.

The 44 patients first treated in the hospital had initial red blood cell counts varying between 1,000,000 and 4,500,000; 10 have either been discharged to other physicians or have been followed for only short periods of time; 34 have been followed for a period of time sufficient for the red blood cells to reach a level of 4,500,000 or more. In order to accomplish this the number of injections of extract derived from 100 gm. of liver (usually 3 cc.*) given generally varied from 5 to 10 and over periods of time varying from 20 to 50 days. The extremes varied from 2 injections in 10 days to 24 in 177 days. The longer periods of time and larger amounts of material were needed in those patients having complicating conditions.

Those treated as ambulatory patients have remained actively at work, some at hard manual labor, throughout their course of treatment. All 15 of this group whose initial red blood cell counts varied between 2,100,000 and 4,000,000 have also been followed until the red blood cell level was 4,500,000 or more. Ten reached this level in from 7 to 50 days and all but 2 in less than 60 days. The amount of liver extract used varied from 1 injection of 3 cc. (derived from 100 gm. of liver) to 8 such injections, except that 1 patient received 13 such injections in a period of 89 days.

In view of the fact that rest is generally considered to be important for the most satisfactory improvement of the blood, it is interesting to note the rapid improvement and the small amount of liver solution used intramuscularly in the ambulatory group. Because the results of treatment have been so little, if at all, retarded by activity it would seem advisable to allow a greater amount of activity for the patients treated in relapse in the hospital, especially the older ones in whom pulmonary complications and phlebitis must be guarded against.

Maintenance Treatment. The aim has been to establish for each patient the optimal treatment necessary for his or her needs and also to be as economical as possible in the amount of material used. It is vastly more important to the patient to be kept in good health than it is to attempt to economize by the use of minimal or suboptimal doses. As with the use of liver substance by mouth, the proper dosage must be determined by the condition of the patient and by the trend of the red blood cell count as recorded at intervals over a period of time. The red blood cell level should remain preferably at or above 5,000,000 cells per c.mm., and the cells themselves should be normal in size and shape. Although the occurrence of symptoms of illness is an important indication of inadequate treatment, the absence of symptoms or a feeling of well-being is neither sufficient evidence that the blood is remaining

* In all but a few of the earlier injections this has been 3 cc. of solution. The earlier solution used and described previously was less concentrated.

normal nor that the patient is in satisfactory condition to avoid progression of the nerve disturbances.

The group of patients under observation has been maintained in a generally better state of health than a similar group observed under oral treatment. This fact is probably to be explained by the relative ease of administering optimal amounts of effective material in a manner favoring better absorption and utilization of the active substance and by the avoidance of gastrointestinal symptoms frequently observed in patients under treatment with liver by mouth, rather than on the basis of some unusual effect of the solution of liver extract. As was noted in a previous paper,[1] improvement in the symptoms occurring with peripheral nerve damage or spinal cord sclerosis has been unusually striking. This effect is no doubt also the result of the rapid and marked improvement possible through the ease of administration of adequate amounts of liver substance by the intramuscular route.

Eighty-one patients have been observed over a sufficiently long period of time to give one a clear idea of their maintenance requirements. This group is made up of 27 of the 44 patients first treated while in the hospital, 12 of those treated as ambulatory patients whose initial red blood cell counts were below 4,000,000, and 42 patients in whom the intramuscular treatment was introduced in place of some other. The red blood cell count when intramuscular treatment was started in the last mentioned group of 42 patients varied between 3,800,000 and 6,800,000. In 20 instances the count was below 4,500,000, and in 13 it was 5,000,000 or more.

In a few instances the lower blood levels in this group were due to failure on the part of the patient to follow out the prescribed treatment either because of an inability to obtain liver or a potent substitute for it, or a temporary inability to ingest it. The majority of those whose recorded initial blood level was below normal were taking average or even unusually large amounts of liver substance by mouth, with failure to maintain a satisfactory physical or blood condition. The difficulty to maintain readily a satisfactory condition with reasonable amounts of material has been due to the presence of chronic infections, arthritis, marked spinal cord sclerosis, unusual worry or perhaps old age. In the remainder of the patients of this group the change to intramuscular treatment has been made in order to influence favorably the difficulties occurring with spinal cord sclerosis, at the request of the patient, usually because of difficulty with the ingestion of the prescribed amount of liver, or through a desire to lessen the expense of treatment.

Typical examples of the manner in which treatment has been carried out in the patients under discussion are shown in Table 1. The red blood cell counts and hemoglobin levels recorded represent only the last determination made before a change to another treatment interval.

The number of patients receiving an injection of 3 cc. (derived from 100 gm. of liver) of the solution of liver extract at the various time intervals is shown in Table 2, together with the extremes and averages of the red blood cell levels in the patients treated at the several intervals.

TABLE 1.—THE MAINTENANCE TREATMENT WITH INTRAMUSCULAR INJECTIONS OF SOLUTION OF LIVER EXTRACT AS CARRIED OUT IN 81 PATIENTS WITH PERNICIOUS ANEMIA.[1]

Case No.	Initial.		7 days.			14 days.			21 days.			28 days.			35 days.		
			No. 7-day intervals.	Resulting.		No. 14-day intervals.	Resulting.		No. 21-day intervals.	Resulting.		No. 28-day intervals.	Resulting.		No. 35-day intervals.	Resulting.	
	R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.
64	4.6	14.5	3	5.2	16.3												
67	4.2	12.8	7	5.6	15.2	3	5.4	14.5									
78	4.3	12.1	3	5.0	13.5	4	5.1	13.9	4	6.1	15.9						
85	4.5	11.7	4	5.2	14.3	5	5.1	14.1	..	..	..	3	5.3	16.3			
92	4.1	13.5	4	4.9	12.8	2	5.2	13.9	2	5.1	14.4	..	..	..	2	5.3	14.1

R.B.C. = red blood cells in millions per cubic millimeter.
HB. = hemoglobin in grams per 100 cc. of blood.

[1] Injections of 3 cc. extract prepared from 100 gm. liver given at the recorded interval.

TABLE 2.—THE INTERVALS BETWEEN TREATMENTS AND THE RED BLOOD CELL COUNTS MAINTAINED WITH INTRAMUSCULAR INJECTIONS OF SOLUTION OF LIVER EXTRACT IN 79 PATIENTS WITH PERNICIOUS ANEMIA.

Interval between injections, weeks.	Number of patients.	Range of final red blood cell counts.*	Average red blood cell counts.*
6	3	4.8–5.7	5.2
5	8	4.6–6.4	5.5
4	11	5.1–6.4	5.6
3	22	4.7–6.1	5.5
2	24	4.5–6.2	5.1
1	11	4.6–5.5	5.2

* In millions per c.mm.

One other patient with an initial red blood cell count of 2,380,000 received injections of solution totaling that obtained from 1000 gm. of liver in a period of 39 days. She has received no further treatment with liver substance during a period of 500 days, during which time her red blood cell count has varied from 5,100,000 to 8,400,000, and the hemoglobin has averaged 16.4 gm. per 100 cc. of blood. Another patient, whose initial red blood cell count was 3,480,000, received 11 injections representing the solution derived from 1100 gm. of liver in 62 days. No further liver treatment has

been received by the patient during a period of 308 days, during which time the red blood cell count has varied between 4,800,000 and 6,100,000 cells and the hemoglobin level has averaged 15 gm. per 100 cc. of blood.

The patients still under treatment at 7- or 14-day intervals have been under treatment generally for shorter periods of time than those receiving treatment at less frequent intervals.

Treatment has been very conservative, and the red blood cell levels have been maintained almost constantly above 5,000,000. In many instances it would no doubt be possible greatly to increase the interval between injections, but for one reason or another this has not been as yet deemed advisable. Because of extraordinarily high red blood cell levels in 2 patients, it has been possible to discontinue treatment for long periods of time. This may prove to be possible in other cases under this form of treatment, but, of course, should only be done when red blood cell counts can be made at frequent intervals.

Storage in the body of the substance active in stimulating formation of the red blood cells is suggested by the result obtained in these 2 patients. Richter, Ivy and Kim[4] have presented evidence which suggests that the liver may have the ability to store the "active principle" of liver, which is in line with the opinion previously expressed by the author[5] that "disturbances in the biliary system or liver may be of even more immediate etiologic importance (in pernicious anemia) than are the gastric changes." Another feature of the treatment has been the frequent occurrence of a steadily increasing red blood cell count as the interval between injections was increased. This suggests that any excess of the active substance over that which is actually used for the immediate production of blood is stored for future utilization.

Reactions. Reactions or complications following the intramuscular injection of the solution of liver extract have been negligible and of little practical importance in this series of cases treated with nearly 1000 injections. Two patients reacted after the first injection, one a small intracutaneous dose, in such a manner that sensitization to liver was suspected. After a series of small doses in increasing amounts both have continued the injections uneventfully. One patient developed urticaria with nausea following the 12th injection given on a very hot day. Very slight urticaria occurred following the next 2 injections, but has not occurred since. This patient first presented herself for intramuscular treatment with generalized urticaria, which had appeared following the ingestion of 2 vials of liver extract (Cohn fraction G). Hare,[2] Strandell and Hammar[3] and others have reported urticarial rashes following the intramuscular injection of various liver extracts. On a few occasions the patient has felt faint after the injection. This has occurred in unusually

nervous persons who have received many other injections without such an occurrence. Hematoma has occurred at the site of injection twice. Infection has not occurred.

Results and Conclusions. Intramuscular injections of the solution of liver extract, given to patients in relapse or whose condition was unsatisfactory because of complications, instigated a remission in each instance, as is to be expected with treatment by means of the ingestion of liver or an actively potent substitute. The beneficial effects of intramuscular injections occurred sooner and more strikingly than with peroral treatment.

Maintenance treatment carried out by the same means in 81 instances for sufficiently long periods of time to allow analysis of the amount of solution needed, shows that an intramuscular injection of the amount of solution derived from 100 gm. of liver (generally 3 cc.), at intervals varying from 1 to 6 weeks, has maintained all of these patients in a satisfactory state of health with a normal condition of the blood. Improvement in the symptoms generally considered to accompany spinal or peripheral nerve damage has occurred regularly and often strikingly, and progression of these disturbances has not occurred in any patient after the blood condition has become essentially normal. Relapse has not occurred in any patient continuing under observation and treatment.

The anemia diet, but not including liver, as previously suggested for the patient with pernicious anemia, has been advised in each instance, and a course of large daily doses of iron (ferric ammonium citrate) has generally been prescribed at some time during the course of treatment, in order to allow the hemoglobin level to keep equal with the course of the rapid red blood cell formation. This has been of distinct benefit in improving the physical condition of the patient.

It has been possible with the use of the intramuscular treatment to maintain this group of patients in a better state of health and with a more satisfactory condition of the blood than was possible by means of treatment by mouth; the prolonged treatment has been more economical to the patient; and this method of administration of liver substance has usually been better liked.

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A STUDY OF A LYMPHOCYTIC HEMOGRAM.

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Arneth,[1] in his monumental work on the polymorphonuclear leukocyte, laid the basis for subsequent studies on the nuclear changes in the granulocyte, culminating in the useful and well-known Schilling index. He also published an index of nuclear variation in the lymphocyte, to which he attached maturative significance. These studies, however, have not been verified.

In a recent article Wiseman[2] has reviewed the criteria of the age of lymphocytes and has classified them as follows:

1. Basophilia of the cytoplasm. The association of basophilia of the cytoplasm with the youth of other blood cells is well known. The so-called reticulocyte is an example of this characteristic in the immature erythrocyte. Basophilia is also well illustrated in the myeloblast and megaloblast.

2. Mitochondria. Cowdry[3] states that as the cell matures, the number of mitochondria diminishes.

3. Size of the cell. This is a subject of considerable controversy, and some authors[4,5] have regarded the large lymphocytes as the younger, while others[6,7,8,9] have considered the small lymphocytes the more youthful. Most investigators studying fixed stained preparations call the large cells older, while those who use supravital technique hold the reverse.

4. Miscellaneous features, such as motility, vacuoles, chromatin content of the nucleus, proportion of nucleus to cytoplasm, shape of nucleus and azure granules.

Wiseman[2] studied normal bloods and those in which he would expect a physiologic or pathologic hyperplasia of lymphoid tissue, such as new-born rabbits and rabbits with active tuberculosis. The degree of basophilia in fixed preparations and the number of mitochondria by the supravital method in the same drop of blood were found to agree. He also found that the shape of the nucleus bears no relation to the degree of basophilia or the number of mitochondria. The chromatin content of the nucleus was not greatest in those cells which were least basophilic. Nucleoli, however, were visible only in the nuclei of cells with deeply basophilic cytoplasm and fine chromatin. No cytoplasmic structure in the living lymphocyte could be identified with the azure granules of the fixed cell, and this suggests that these granules are a precipitation brought about by fixation, possibly evidencing some functional

TABLE 1.—NORMALS.

Case.	Sex.	Age.	Diagnosis.	Date.	W. B. C.	Neut. polys., per cent.			Lymph., total per cent.	Lymph., per cent.			Mon., per cent.	Eos., per cent.	Bas., per cent.	Clinical data.
						Young.	Band.	Mature.		Yg.	Med.	Old.				
		20–40	Average of normal adults	..	7,000	..	4	63	25	5	50	45	7	1	0	25 cases.
		1–12	Average of normal children	..	8,000	..	2	41	50	10	60	30	5	1	1	25 cases.
		1–12 mos.	Average of normal infants	..	10,000	..	2	28	59	10	65	25	8	2	1	25 cases.
1	M	32	Normal	10/6	7,000	..	1	69	23	17	45	38	6	..	1	Well.
				10/8	7,000	..	3	75	14	14	72	14	6	2	..	Head cold; temp. 100°.
				10/12	4,800	..	..	64	32	15	59	26	1	2	..	Well.
				10/14	5,200	..	3	54	38	6	55	39	4	..	1	Well.
				10/29	6,800	..	1	57	35	8	54	38	6	1	..	Well.
				11/4	7,000	..	..	63	26	8	54	38	11	..	..	Well.
2	F	30	Normal	10/15	8,000	..	1	61	30	3	41	56	7	1	..	Well.
				10/28	11,200	..	2	71	20	5	45	50	6	..	1	Well.
				11/4	8,100	..	1	58	35	9	66	25	6	..	..	Cold.
				11/9	9,600	..	..	60	33	11	58	31	3	4	..	Pains in abdomen for
				11/11	5,100	..	..	48	43	10	60	30	7	1	1	1 week; up and
				11/15	11,000	..	1	60	35	5	64	31	1	1	2	about.
				11 18	5,400	..	..	48	38	11	52	37	10	4	..	Well.

TABLE 2.—LEUKEMIC CASES.

Case.	Sex.	Age.	Diagnosis.	Date.	W. B. C.	Neut. polys., per cent.			Lymph., total per cent.	Lymph., per cent.			Mon., per cent.	Myelocytes, per cent.	Premyelocytes, per cent.	Myeloblasts, per cent.	Clinical data.
						Young.	Band.	Mature.		Yg.	Med.	Old.					
1	M	58	Lymphatic leukemia	10/15	200,000	..	2	13	85	95	5	0					
2	M	10	" "	8/2	31,000	..	..	8	92	60	35	5					
3	M	55	" "	9/3	42,800	..	..	25	73	39	51	10	2				
4	M	19	" "	10/18	5,000	..	..	19	77	78	22	0	2	2	..	..	Lymphoblasts, 34 per cent; died in 2 mos.
5	M	60	" "	7/20	140,000	..	..	7	92	0	100	0	1	..	..	..	Left hospital.
6	M	62	" "	10/5	120,000	..	..	1	99	0	100	0	..	..	..	..	Chronic type.
				10/22	170,000	..	2	2	96	0	97	3	..	..	..	..	Blasts, 20 per cent.
				10/29	150,000	..	..	2	98	0	95	5					
				11/5	150,000	..	..	2	97	0	96	4	1				
7	M	59	Myeloid leukemia	8/20	100,000	..	..	2	.. (on exam.	20 many fie	80 lds)	0	..	10	10	78	Acute form.
8	F	60	" "	8/31	6,000	..	..	18	25	30	64	6	..	2	1	54	Subacute form.
9	M	36	" "	9/12	30,000	..	..	8	14	35	65	0	..	5	..	73	Subacute form.
10	M	45	" "	9/20	300,000	15	20	24	.. (on exam.	8 many fie	80 lds)	12	..	17	22	2	Chronic form.

TABLE 3.—OTHER DISEASES.

Case.	Sex.	Age.	Diagnosis.	Date.	W. B. C.	Neut. polys., per cent.			Lymph., total per cent.	Lymph., per cent.			Mon., per cent.	Eos., per cent.	Bas., per cent.	Clinical data.
						Young.	Band.	Mature.		Yg.	Med.	Old.				
1	F	18	Appendiceal abscess	9/24	9,600	12	60	14	5	60	40	0	9	..	..	Rise of temp. to 104° after appendectomy, done 9/21.
			Operation	9/29	17,000	5	39	30	22	50	31	19	4			
				10/1	11,400	5	28	44	16	37	56	7	7	..	..	Very toxic.
				10/4	15,400	6	50	28	10	0	100	0	6	..	..	Abscess found in pouch of Douglas; reoperated, 10/6.
				10/8	17,000	..	22	52	17	41	41	18	8	..	1	
				10/11	14,800	..	11	70	15	14	66	20	3	1		
				10/15	16,800	..	2	52	37	32	59	9	7	2	..	Gradual improvement.
				10/20	9,800	..	8	63	22	43	51	6	2	4	1	
				10/24	8,000	..	2	39	56	4	74	22	2	1		
				10/27	9,000	..	1	54	39	21	55	24	4	..	2	Discharged.
2	F	32	Meningococcus meningitis	10/24	32,000	..	19	70	6	16	84	0	5	..	..	Very sick.
				10/27	20,000	..	9	83	5	80	20	0	3	..	..	Died.
3	M	24	Pulmonary tuberculosis	10/5	6,400	..	3	83	5	60	20	20	8	..	1	Temp. 103°; pneumothorax and insulin treatment.
				10/12	9,800	..	6	72	13	23	46	31	9	..	..	Temp. 101°.
				10/22	12,400	..	3	26	57	5	59	36	6	6	2	Temp. 100°.
				10/29	9,000	..	2	58	29	7	55	38	6	4	1	Temp. 99°.
4	F	52	Pernicious anemia	9/26	4,000	..	3	58	26	30	63	7	11	2	..	Hb., 50 per cent; R.B.C., 2 millions; temp. 102°.
				9/29	10,000	..	3	68	23	9	71	20	1	5	..	Given injections of liver extract;
				10/3	8,800	..	3	66	20	5	65	30	8	1	2	impr.; temp. 99°; went home.
5	M	21	Lung abscess	10/22	26,400	..	13	44	40	5	60	35	3	..	..	Patient very sick.
				10/26	30,600	3	30	42	21	57	28	15	4	..	..	Developed empyema, thoracotomy done.
				10/29	29,800	..	21	50	28	20	52	28	1			
				11/2	20,800	5	39	36	19	52	31	17	1	..	..	Died.
6	F	42	Influenzal bronchopneumonia	10/18	7,000	..	9	57	30	10	54	36	4			
				10/21	11,600	..	8	47	38	0	53	47	6	..	1	Temp. 101°.
				10/25	9,600	..	2	43	55	2	75	23	..	..	..	Gradually improved.
				10/28	6,200	..	2	49	45	11	51	38	3	..	1	
				11/1	10,000	..	2	67	25	4	44	52	4	..	2	Discharged.
7	M	5	Intestinal intoxication	10/19	13,600	..	10	74	12	33	58	9	4			
				10/21	15,400	..	7	67	23	9	78	13	..	1	2	Temp. 101°.
				10/25	11,200	..	2	37	55	3	88	9	3	2	1	Improved.
				10/28	9,800	..	..	46	48	6	72	22	3	2	1	
				11/1	13,000	..	1	45	44	18	52	30	4	6	..	Discharged.
8	F	1½	Nutritional secondary anemia	10/18	8,600	..	4	44	50	10	90	0	..	1	1	Hb., 30 per cent; temp. 101°.
				10/21	9,800	..	1	29	56	16	60	24	5	6	3	Transfusion given.
				10/25	11,200	..	..	25	64	15	70	15	3	3	5	Improved with iron and liver pulp.
				10 28	10,400	..	2	32	58	10	70	20	5	3		
				11 1	11,200	..	1	45	37	5	70	25	9	6	2	
				11 4	7,000	..	1	53	33	11	46	43	11	1	1	Hb. 70 per cent; discharged.
9	M	35	Inguinal adenitis; etiology unknown	10 7	6,000	..	5	41	49	28	51	21	4	..	1	Temp. 100.5°; slight chills.
				10 12	7,800	..	1	66	23	26	52	22	7	1	2	Improved.
				10/21	7,600	..	4	40	47	4	55	41	7	2	..	Improved.

10	M	36	Multiple neuritis; etiology unknown	9/22	17,000	..	3	28	11	0	70	30	3	54	1	Temp. 101°; biopsies for trichiniasis negative.
				9/26	16,000	..	..	32	8	0	75	25	3	56	1	
				9/29	12,800	..	..	37	9	0	78	22	1	53		
				10/3	16,600	..	..	44	12	41	50	9	3	40	1	Temp. 100°.
				10/6	15,600	..	..	39	13	38	62	0	3	44		
				10/10	16,400	..	..	37	6	0	84	16	5	52		
				10/20	13,400	..	..	25	12	33	50	17	3	59	1	
				10/27	12,200	..	..	53	15	54	46	0	2	25	1	
				11/3	20,000	..	..	33	10	60	22	18	3	54	..	Unimproved.
11	F	52	Carbuncle of upper lip	10/29	32,200	..	17	71	6	16	68	16	6	..	..	Temp. 104°.
				11/2	28,700	3	32	60	4	25	75	0	1			
				11/5	53,600	..	23	67	8	37	63	0	2	..	..	Progressively worse.
				11/9	30,800	..	8	87	5	51	49	0				
				11/12	32,600	2	8	82	6	58	33	9	2	..	..	Died.
12	M	43	Inguinal adenitis	10 22	14,800	..	19	50	25	4	48	48	4	1	1	In hospital since 8/2, running septic temp.; biopsy of gland showed enormous proliferation of endothelial cells; temp. now between 99 and 100°, feels well.
				10/26	9,500	..	5	59	29	3	53	44	7			
				10/29	16,600	..	2	56	36	0	34	66	2	4		
				11/5	7,800	..	2	48	40	2	33	65	7	2	1	
				11/16	11,000	..	3	37	46	3	35	62	9	4	1	
13	M	39	Typhoid?; bronchopneumonia	10/22	7,000	..	2	55	41	9	40	51	2	..	..	Temp. 101°.
				10/26	9,400	..	2	68	23	22	56	22	7	..	..	History and Widal suggestive of typhoid; developed signs in chest.
				10/29	6,800	..	7	71	17	12	50	38	5			
				11/2	7,400	..	0	61	34	36	35	29	5			
				11/5	8,600	..	4	48	38	5	45	50	10	..	..	Improved.
				11/9	5,600	..	6	75	15	20	33	47	3			
				11/12	4,000	..	6	38	52	18	42	40	3	..	2	
				11/16	5,400	..	5	58	36	3	27	70	1	..	..	Improved.
14	F	44	Pneumonia; aneurysm of aorta or possible mediastinal neoplasm	10/22	26,200	..	6	76	8	12	62	26	9	..	1	Temp. 102°.
				10/26	19,000	..	4	72	17	15	56	29	7			
				10/29	16,400	..	2	60	27	18	51	31	10	..	..	Gradual improvement; temp. 100°.
				11/2	13,200	..	2	68	19	31	47	22	9	1	1	
				11/5	8,400	..	..	43	44	29	42	29	11	2	..	Slight relapse; temp. 103°.
				11/9	18,800	..	..	88	9	22	56	22	3			
				11/12	6,600	..	..	42	47	12	34	54	10	..	1	Improvement; temp. 100°.
15	F	10	Chronic osteomyelitis of right femur	10/21	16,400	..	..	53	37	8	67	25	3	3	2	Temp. 100.5°.
				10/25	24,000	..	4	63	29	3	70	27	3	1		
				10/28	23,800	..	1	63	26	3	57	40	5	5		
				11/1	13,400	..	5	59	27	27	59	14	6	3	..	Temp. 101°; slight operation.
				11/4	15,000	..	3	52	42	26	33	41	2	1		
				11/10	9,800	..	..	37	56	10	44	46	2	3	2	
				11/17	15,400	..	..	47	42	7	28	65	2	9	..	Temp. 99°.
16	M	48	Lobar pneumonia	11/1	7,000	..	7	81	6	16	68	16	6	..	..	Type I pneumococcus; temp. 103°.
				11/4	7,600	..	1	67	29	10	63	27	3			
				11/7	7,200	..	4	50	40	35	45	20	6	..	..	Improved.
				11/10	4,400	..	1	45	45	13	70	17	5	1	3	
				11/14	6,400	..	..	62	36	11	41	48	..	2	..	Up.
17	F	21	Grippe	11/1	10,000	..	..	60	29	24	73	3	9	2	..	Temp. 101.5°.
				11/4	15,200	..	..	58	30	16	61	23	9	3		
				11/9	10,300	..	..	44	49	12	67	21	5	1	1	Temp. 100°; menstruating.
				11/11	11,600	..	..	48	47	49	36	15	4	1		
				11/15	14,200	..	1	62	29	20	41	39	6	1	1	Improved; temp. 99°.
				11/20	8,000	..	3	61	26	7	50	43	7	3	..	Well.

activity of the mature cell. It, therefore, seems that basophilia of the cytoplasm is a constant and reliable criterion of the age of lymphocytes.

With these facts in mind studies were undertaken on a series of normal and diseased adults and children to see if a classification of lymphocytes according to the degree of basophilia would be of clinical value.

The cases selected were widely diversified and represented all types, from the very sick to ambulatory patients with minor complaints. In establishing the normals, single observations were used in the majority of instances. The sick patients were studied at bi-weekly intervals during their stay in the hospital, and a small series of normals were followed at similar intervals over a time interval corresponding to the average stay of a patient in the hospital.

This report embodies 75 normals, equally divided among adults, infants and children, 10 normals followed at bi-weekly intervals for 1 month and 150 patients followed at bi-weekly intervals during their stay in the hospital.

Technique. White and differential counts were done for each observation. The total white counts were done with carefully standardized pipettes, and the films were made on slides, care being taken to keep them "rim free." The stain used was Wiseman's Wright-Giemsa. An average of 200 leukocytes was counted and the lymphocytes were divided into three classes: Y (young), M (medium) and O (old) forms, according to the degree of basophilia of their cytoplasm. The Y forms have a deep blue cytoplasm, the M forms moderately blue and the O forms are faintly blue or colorless, and usually show azure granules in the cytoplasm, although the M forms occasionally show them too. A little practice with the above technique will make the three divisions clear. It is necessary, however, that the lymphocytes be examined in those parts of the film in which the red cells do not overlie, as in the thick portions of the film the lymphocytes are likely to overstain. The total number of lymphocytes is noted as well as the number of Y, M and O forms, and the percentages of each are then easily calculated, the procedure being similar to that followed in enumerating the different forms of polymorphonuclears when doing the Schilling index. When the total number of lymphocytes is low it is best to count 300 to 500 white cells to insure more accurate results. The polymorphonuclear leukocytes were tabulated according to the Schilling method in each instance in order to compare the granulocytic and lymphocytic indices.

The observations are to be found in the Tables, pages 279 to 281.

Discussion. Analysis of the experimental data shows that there is a fairly constant lymphocytic formula for normals. For adults this can be expressed as Y forms, 5 per cent; M forms, 50 per cent; O forms, 45 per cent. Variations occur in this formula under different conditions, and we can, therefore, speak of a shift to the left or to the right of the lymphocytic index, depending upon whether the number of younger forms is greater or less than normal. A comparison with the Schilling index in each case shows that the two do not run parallel. The lymphocytic index is not as stable as the Schilling and will shift to the left just as easily in a mild

as in an acute infection. Even though the lymphocytic formula cannot be used to gauge the severity of an infection, its shift to the left in these conditions nevertheless indicates that lymphocytes take an active part in combatting bacterial invasion. This is seen by the increase in Y and M forms and the decrease in O forms in practically all cases of infection.

The lability of the lymphocytic hemogram makes it valuable in the detection of minor infections which do not disturb the more stable Schilling index. Interesting and confirmatory evidence for using basophilia as a criterion of the age of lymphocytes is seen in the study of the lymphatic leukemias. The marked increase in the proportion of Y and M forms in these cases represents the well-known hyperactivity of the lymphatic system in these diseases. In the myeloid leukemias there is also an increase in lymphocytic activity and a shift of the index to the left.

It is also of interest to note that, according to the lymphocytic index, most patients are not entirely well on being discharged from the hospital and that the period of convalescence is probably much longer than usually expected. A patient should not be regarded as entirely recovered from an infection until the lymphocytic formula has returned to normal.

Conclusions. 1. A lymphocytic hemogram has been studied, using basophilia of the cytoplasm as a criterion of the age of the lymphocytes.

2. The lymphocytic formula is stable in health, but is more labile than the Schilling index, and cannot be used to gauge the severity of an infection. Its shift to the left in infections nevertheless indicates that the lymphocytes take an active part in combatting these conditions.

3. The lability of the lymphocytic index makes it valuable in detecting minor infections which do not disturb the more stable Schilling index.

4. The lymphocytic index is superior to the Schilling in guarding the progress of convalescence, and a patient should not be regarded as entirely well until the lymphocytic formula has returned approximately to normal.

Grateful acknowledgment is due Dr. J. S. Leopold for permission to study cases from the A. Jacobi Children's Division, Lenox Hill Hospital.

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REVIEWS.

A Standard Classified Nomenclature of Disease. Compiled by The National Conference on Nomenclature of Disease. Edited by H. B. Logie, M.D., C.M., Executive Secretary. Pp. 701. New York: The Commonwealth Fund, 1933. Price, $3.50.

The names of the organizations and their distinguished representatives that have aided in or approved of this compilation are as good a guarantee of its value as such evidence can be. In passing one cannot help being curious why pathology was not included in the conference members or coöperating committees. Surely here is a field in which the pathologist has the last and most decisive say!

While one can naturally find many single items for objection, the general scheme is excellent. Using the decimal system throughout, a topographical classification (to 3 or more decimals) begins on page 14, giving 11 main systems (0, body as a whole; 1, integumentary; 2, musculo-skeletal, etc.). On page 50 begins the etiological classification, again with 11 subdivisions (0, prenatal; 1, lower parasites, etc., through x, "unknown or uncertain, the functional reaction to which alone is manifest"). Thus from the classified nomenclature proper (beginning on page 83) we learn for example that *talipes equinus* is listed as 249–0225, *i. e.*, a disease of a joint (24) ninth to be listed, which is an abnormality of structure (02) due to distortion (022), the fifth to be listed (0225). The full index and especially "How to Use the Nomenclature" (page 11) should first be consulted.

E. K.

Endocrine Medicine. In four volumes. By William Engelbach, M.D., F.A.C.P., B.S., M.S., D.Sc., Member of Starr, St. Louis, City, Jewish, Baptist Sanitarium and Maternity Hospitals. With a Foreword by Lewellys F. Barker, Professor Emeritus of Medicine, The Johns Hopkins University School of Medicine, Baltimore. Vol. I. General Considerations. Pp. 460; 139 illustrations and 62 tables. Vol. II. The Infantile and Juvenile Endocrinopathies. Pp. 473; 109 illustrations and 25 tables. Vol. III. The Adolescent and Adult Endocrinopathies. Pp. 862; 255 illustrations and 26 tables. Vol. IV. Bibliography, Index of Names and Subjects. Pp. 117. Springfield, Ill.: Charles C Thomas, 1932. Price, $35.00 a set.

This is an elaborate treatise on endocrinology, with special emphasis placed on thyroid and pituitary, the author having reserved for the future a discussion (which his unfortunate death now prevents) of the islands of Langerhans and of Addison's disease.

Everyone must agree with the author's opening statement that "The recent advances made in the studies of the physiology and pathology of the endocrine glands are considered sufficient justification for compilation of a treatise endeavoring to bring this subject up to date." One would hope, too, that a four-volume work could give a satisfactory summary of the present knowledge of the various phases of this complex subject, even though doubting any one individual's ability to present all the different aspects satisfactorily. We must admire the author's courage, therefore, in undertaking the job single-handed, if not unaided, even though we may recognize that not a few questionable personal interpretations shake one's confidence in the value of the whole production.

Much of the literature is reviewed in a manner that is both careful and up to date, but the discussion is chiefly based upon the author's records of over 2000 patients with endocrine disorders. Thus the Fundamentals—whose advances constituted the "sufficient justification"—occupy but 200 of the 1800 pages of text. Furthermore the method of approach renders consultation arduous, even though the extensive index facilitates search for a given item. The segregation of the individual gland disturbances—often into different volumes—into disorders arising in Infants, Juveniles, Adolescents and Adults, makes a connected survey from the anatomical standpoint difficult and necessitates considerable repetition.

The work is profusely illustrated with photographs of patients, Roentgen rays, charts and detailed case histories. It is of interest in expressing the experience, convictions and classifications of the clinician author, and with its many references to the literature should be valuable to workers in this field. E. K.

A Manual of Embryology. By J. Ernest Frazer, F.R.C.S. Eng., Professor of Anatomy in the University of London; Lecturer at the Medical School of St. Mary's Hospital, etc. Pp. 486; 282 illustrations. New York: William Wood & Co., 1932. Price, $8.00.

Even when existing textbooks on a subject are being kept reasonably up to date, a good new work is almost bound to bring a fresher point of view and give more adequate treatment to recent developments. In this case, the distinguished author is especially qualified to present the advances of the last quarter century in explaining the processes of development of human organs and tissues. The regional method of approach has been followed, as giving a better "connected mental picture of the developing embryo." Nevertheless a good index—and we commend the black face figures to indicate the chief treatment of a topic—permits one to use the book up to a certain point as a work of reference. All references, however, are omitted, statements made on the authority of others merely being indicated by the author's name in a bracket. Even for the medical student for whom the book is intended this constitutes a grave handicap for broad-minded study. However, even with this restriction, the book will prove useful in medical schools. E. K.

Men Against Death. By Paul deKruif. Pp. 363; illustrated. New York: Harcourt, Brace & Co., 1932. Price, $3.50.

Like the Microbe Hunters, Men against Death makes mighty good reading (so contagious is the author's style that an expletive unwittingly slipped in here, only to be replaced by the weaker adjective on re-reading!). We hope that a multitude of medical students and laymen will form the same opinion, so that they may become personally acquainted with more of the outstanding figures of our medical history. After this expression of our feelings, we hope that some objective criticisms will not be misunderstood.

A book which "pretends only to tell the plain story of scientific adventure for plain people" naturally must be evaluated by different criteria than a work of biography or history. We can pass over, then, more easily the colorful hyperbole and gratuitous expletives that are apparently deemed necessary to enliven the narrative, and, hoping that the facts have not been stretched to make a good story, can look forward to instructive entertainment. The author's prologue on the theme of his intense desire to live longer, like the cover advertisement that the book "is for all who want

to stay young as long as they can," should undoubtedly be read with the tongue in the cheek, but what odds to the modern reader, if amusing! Those described are: "Semmelweiss: a tragic man afire to find a safe way to help mothers have their babies; Banting: brought new strength to people whose lives were running away in rivers of sugar; Minot: tricked pernicious anemia. Before him it was inexorably fatal; Spencer: found an unprecedented and fantastic way to guard men from spotted fever; Evans: removed one great danger lurking in the American milk supply; McCoy: fighting parrot fever alone, a general who did not want to die in bed; Schaudinn: discovered the pale horror of the sickness which along with cancer is one of humanity's two worst enemies; Bordet: spotted the pale horror's hiding; foretold doom for those neglectful; gave hope to all who'd fight their fate; Wagner-Jauregg: his friendly fever, now the electric fever of the new machine medicine, burns out paresis; Finsen: the Dane who trapped the light of the sun; Rollier: showed the folly of men spending millions to get themselves well when with free Doctor Sun they'd never start to be sick; Strandberg: turned Finsen's machine-sun on TB's most desperate consequence." The author has been able to amplify his sketches by personal contact with nine of the twelve subjects, which gives the reader a sense of closer contact than with the more remote figures of the Microbe Hunters.

E. K.

SCIENCE AND SUPERSTITION IN THE EIGHTEENTH CENTURY. A Study of the Treatment of Science in Two Encyclopedias of 1725–1750. Study No. 364 in Studies in History, Economics and Public Law, Edited by the Faculty of Political Science of Columbia University. By PHILIP SHORR, PH.D. Pp. 82. New York: Columbia University Press, 1932. Price, $1.50.

To determine the amount of pseudoscience still clinging to science after the glorious 17th century, the author has examined the way in which science was handled in two representative 18th century encyclopedias—Chambers' Cyclopedia (London, 1728) and Zedler's Universal Lexicon (Leipzig, 1732–1750). Together with Thorndike's similar study of Diderot's Encyclopédie, these constitute "a key to the habits of thought" in science in the three leading countries of Europe. The two encyclopedias are considered separately, necessitating a certain amount of repetition and of division of attention. Thus although the treatment of astronomy by Pythagoras, the Arabians and so forth is considered in Chambers' work, the same has to be taken up again with variations in Zedler's. In medicine, we learn that the work begun by Vesalius and Harvey had had but little influence on scientific thought in overthrowing medieval Galenism—"The two encyclopedias still bear a close resemblance to their earlier medieval prototypes."

E. K.

ANLEITUNG ZUR FRÜHZEITIGEN ERKENNUNG DER KREBSKRANKHEIT. By various contributors. Pp. 134. Leipzig: S. Hirzel, 1932. Price, Rm. 3–.

THIS symposium on the early diagnosis of cancer has been written for the use of the general practitioner. It places the responsibility for the successful control of this disease in his hands. The early stigmata of cancer and certain general diagnostic procedures such as the sedimentation time are discussed first. There is next a very detailed review of cancer and sarcoma and its origin from the different epithelial and connective tissues. The larger part of the booklet is devoted to a detailed study of malignancy of every region,

organ and system of the body. Special stress is laid on a few early signs of cancer which should arouse the suspicion of the physician. Naturally the most frequent carcinomata such as carcinoma of the stomach, rectum, cervix and breast receive the most attention. The prognosis, without treatment and with early treatment, and the very earliest and most highly specialized diagnostic procedures are discussed at length. Such a dictum as: "The early diagnosis of malignancy in the small intestines is made by luck, in the large bowel by skill, and in the rectum as a matter of duty" is typical of the many of its phrases. It will be useful in the instruction of both student and general practitioner. I. R.

ANTONY VAN LEEUWENHOEK AND HIS "LITTLE ANIMALS." By CLIFFORD DOBELL, F.R.S., Protistologist to the Medical Research Council, London; Foreign Member of the R. Accádemia dei Lincei, Rome; Sometime Fellow of Trinity College, Cambridge. Pp. 435; illustrated. New York: Harcourt, Brace & Co., 1932.

THIS excellent work—the result of 25 years' personal study—comes opportunely from one of the leading protozoölogists of his day on the 300th anniversary of the birth of the great Dutch microscopist. Finding commentaries more misleading than helpful, the author had chief recourse to Leeuwenhoek's copious correspondence in colloquial Dutch with the Royal Society of London, still extant in their archives. Tedious effort in mastering the difficult script (see Plate 5) as well as the archaic language has revealed much of interest about the man as well as his work that was not previously available. His letters from the first one, sent at the instigation of de Graaf, down to the last, sent on his deathbed a half century later, "contain observations on matters zoölogical, botanical, physical, physiological and miscellaneous (unclassifiable). They are mostly . . . . concerned with observations and discoveries made with the microscope."

Following a hundred well-documented pages about Leeuwenhoek's life, methods of work, family relations, contemporary estimates and such like, come two hundred pages of translated letters, with numerous notes and comments. More notes on various personal items, including 27 "lost" letters found by Dobell, are followed by a critical evaluation of Leeuwenhoek's position in science, resulting in the conclusion, which would be hard to controvert, that he is justly regarded as the Father of Protozoölogy and Bacteriology. While the author's notes and comments would in themselves constitute a distinct contribution to the history of science, even more valuable are the original researches and translations now available for the first time. Dobell's successful attempt to preserve the quaintness of the original text, as far as compatible with maintaining the meaning conveyed by their originator, lends further charm to the presentation, still more added to by a strain of old-fashioned humor that pervades the comments and especially the Epistle to the Reader. E. K.

OFFICE SURGERY. By FENWICK BEEKMAN, M.D., Visiting Surgeon, Bellevue Hospital; Visiting Surgeon, Hospital for the Ruptured and Crippled, etc. (Everyday Practice Series, edited by HARLOW BROOKS, M.D.) Pp. 402; 94 illustrations. Philadelphia: J. B. Lippincott Company, 1932. Price, $5.00.

THE volumes in this series are prepared primarily for the general practitioner. The cover and format are well done. The author has aptly said

that "there is no such thing as minor surgery for any surgical lesion, be it ever so insignificant, may be the first sign of a serious condition." The form and style in which the subjects have been presented are not strictly conventional, but the author has attempted to "present a readable book." The material for use in an office, anesthesia, wounds, fractures and dislocations, infections, superficial neoplasms and lesions of the external genitalia, anus and rectum are covered in an interesting, terse fashion. The illustrations are good. This volume should prove a valuable addition to the literature of the student and general practitioner. I. R.

FUNCTIONAL DISORDERS OF THE LARGE INTESTINE AND THEIR TREATMENT. By JACOB BUCKSTEIN, M.D., Instructor in Gastro-intestinal Roentgenology, Cornell University Medical College, etc. Pp. 223; 60 illustrations and 40 reproductions of radiographs. New York: Harper and Brothers, 1932. Price, $3.00.

THE author has been peculiarly successful in preparing a concise book on the functional disorders of the colon. Our understanding of this organ has been chiefly advanced in recent years by roentgenologic studies and full use of these is made throughout. Detailed instruction in the handling of patients is made to depend whenever possible upon the fundamental pathologic physiology as far as it is understood. Specific information which the practitioner requires is here readily accessible upon such subjects as constipation, enteroptosis, "irritability of the colon associated with mucus," gaseous distension, and the perennial question of chronic appendicitis. The symptoms generally attributed to these conditions are of such great frequency, and the conditions, themselves, so ill-defined, that the experimental approach to their explanation becomes particularly valuable. In the case of the colon, this has been difficult because of the inconsistency of response which characterizes that organ. The experimental data, therefore, are frequently contradictory, and one could wish that even at the expense of compactness the author might more frequently have given his own conclusions from the evidence he presents.

Taken as a whole, the book is well balanced, though one is occasionally surprised, as by the space allotted to studies of such debatable value as the roentgenologic diagnosis of chronic appendicitis. Nevertheless, it is a careful attempt briefly to clarify a very involved field of medicine.

W. O. A.

RADIOLOGIC MAXIMS. By HAROLD SWANBERG, B.Sc., M.D., F.A.C.P., Editor, The Radiological Review; Radiologist, St. Mary's Hospital and Blessing Hospitals, Quincy, Ill., etc. With a Foreword by HENRY SCHMITZ, A.M., M.D., LL.D., F.A.C.R., F.A.C.S., Professor of Gynecology and Head of the Department, Loyola University School of Medicine, etc. Pp. 125. Quincy, Ill.: Radiological Review Publishing Company, 1932. Price, $1.50.

A LITTLE volume devoted to a heterogeneous collection of radiological principles gathered from the rapidly accumulating knowledge of the use of radium and the Roentgen ray. Included are numerous quotations from various medical authorities relative to the value of radiology and the position it now occupies in the realm of medical diagnosis and treatment.

K. K.

MANUALE DI ANALISI CHIMICA. By CESARE SERONO, Dattore in Medicina ed in Chimica; Docente in Chimica e Microscopea Clinica nella R. Università di Roma. In collaboration with PROFESSOR ALFONSO CRUTO. Pp. 483; 85 illustrations. Second edition, Torino: Unione Tipografico-Editrice Torinese, 1932. (Price not given.)

THE outstanding feature and advantage of this manual over similar publications is the general part dealing with elementary chemical procedures, containing data valuable to the laboratory worker. The special part covers complete chemical examination of blood, urine, feces and other excreta and secreta. In addition there are good chapters on food and water analysis, and analysis for the commonest poisons. M. S.

RESEARCHES ON BLACKWATER FEVER IN SOUTHERN RHODESIA. No. 6 of the Memoir Series of The London School of Hygiene and Tropical Medicine. By G. R. ROSS, M.B., CH.B., PH.D., D.P.H., Rhodesian Research Fellow, London School of Hygiene and Tropical Medicine. Pp. 262; illustrated with tables and charts. London: The London School of Hygiene and Tropical Medicine. Price: paper, 8s.; cloth, 10s.6d.

IN his interesting studies Dr. Ross brings out the epidemiology, blood changes, treatment, etc., in patients suffering with blackwater fever. There should not be any fixed outline of treatment, however, as no two cases are alike, and the author is of the opinion that each patient should be treated individually. D. DER.

THE FAILING HEART OF MIDDLE LIFE. By ALBERT S. HYMAN, A.B., M.D., F.A.C.P., Cardiologist, Beth David and Manhattan General Hospitals, etc., and AARON E. PARSONNET, M.D., C.M., F.A.C.P., Attending Physician and Cardiologist, Newark Beth Israel Hospital, etc. With a Preface by DAVID RIESMAN, M.D., Sc.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine. Pp. 538; 166 illustrations, some in colors. Philadelphia: F. A. Davis Company, 1932. Price, $5.00.

THE authors of this volume have limited themselves almost exclusively to a consideration of those cardiac manifestations that result from a derangement of the blood supply of the heart. The various phases of the subject have been fully and comprehensively discussed. The book is well made up and contains many good illustrations. The style is to be both criticized and commended; it is at times labored and involved and even redundant; but in spite of these handicaps, the book proves easy and pleasant to read.

Many of the conclusions are highly speculative. Some, particularly those based upon a wide application of the theory of functional stenocardia or coronary insufficiency, will not be definitely accepted at the present time by many students of cardiology. However, such hypothetical conceptions do no real harm if they are understood to be tentative; nor do they prevent the book from fulfilling its real purpose. This, as admirably set forth in the preface by Riesman, is to present comprehensively this very important subject to the general practitioner and "to maintain his confidence in himself while at the same time urging him to become acquainted as far as possible with the newer science of cardiology." This aim is well fulfilled. T. MCM.

THE 1932 YEAR BOOK OF RADIOLOGY: DIAGNOSIS. Edited by CHARLES A. WATERS, M.D., Associate in Roentgenology, Johns Hopkins University; Assistant Visiting Roentgenologist, Johns Hopkins Hospital. THERAPEUTICS. Edited by IRA I. KAPLAN, B.Sc., M.D., Director, Division of Cancer, Department of Hospitals, City of New York, etc. Pp. 750; 498 illustrations. Chicago: The Year Book Publishers, Inc., 1932. Price, $6.00.

IN this volume is given a brief review of the principal American and foreign contributions made to radiologic literature during the past year. Of its two parts, the first is devoted to diagnosis and the second to therapy, edited by Drs. Waters and Kaplan, respectively. The authors have succeeded in presenting a concise and comprehensive résumé of the progress made in radiology during the past 12 months. Numerous illustrations and individual references to the original articles add materially to the value of this work. This volume should be appreciatively welcomed by those engaged in the practice of radiology, as it affords an excellent panoramic view of the present status of this specialty. K. K.

THE HISTORY OF DERMATOLOGY. By WILLIAM ALLEN PUSEY, A.M., M.D., LL.D., Professor of Dermatology Emeritus, University of Illinois; sometime President of the American Dermatological Association and of the American Medical Association. Pp. 223; 32 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $3.00.

THE author, himself an eminent dermatologist, has produced for English speaking readers an account of dermatology that has previously been available only in such works as Puschmann's *Handbuch*, Richter's *Geschichte der Dermatologie* or in the short introductory chapters of textbooks or scattered through general medical histories. Believing that one should especially study the masters, he has included more than 300 individuals in the 9 chapters that chronologically divide the story of dermatology between 3000 B.C. and modern times. More than half the space is required for the 19th and 20th centuries, however. Though there is considerable space devoted to matters that have little to do with dermatology, this will doubtless not be objected to by the general reader. A novel and most useful feature is a 35-page Historical Index by Dr. Herbert Rattner, which without pretending to absolute completeness gives significant data about skin disease, arranged alphabetically. The book is in Thomas' accustomed high level of bookmaking, excellent paper, type (21 by 38 pica) and binding that makes it a delight to handle. It is, however, no exception to the dictum that the book without an error has never been printed. The illustrations are well chosen and for the most part excellent. E. K.

A GUIDE TO HUMAN PARASITOLOGY. By D. B. BLACKLOCK, M.D. (EDIN.), D.P.H. (LOND.), D.T.M. (LIVER.), Professor of Parasitology, Liverpool School of Tropical Medicine, the University of Liverpool, etc., and T. SOUTHWELL, D.Sc., PH.D., A.R.C.Sc., F.Z.S., F.R.S.E., Lecturer in Helminthology, School of Tropical Medicine, Liverpool, etc. Pp. 271; 122 illustrations, and 2 colored plates. New York: William Wood & Co., 1932. Price, $4.00.

THIS is a well-written, carefully arranged and unusually complete manual. The opening chapters are devoted to discussions of readily available sources

of material for study; simple but practical and accurate means of diagnosis; the mechanics of the microscope, and its care, calibration and use; methods of examining material such as blood, feces and urine for parasitic organisms; and general phases of parasitology and nomenclature. This is followed by sections on spirochetes, protozoa, cestodes, trematodes and nematodes parasitic in man. There is a chapter on myiasis and one giving tabulated summaries of life histories, vehicles of transmission, modes of infection, tissues involved and diagnostic characters. The last hundred pages contain notes on the therapy of parasitic diseases, a list of apparatus and reagents that may be of value, a short list of reference books and an index. The sections dealing with each group of organisms open with general statements, definitions, keys for identification and diagnostic methods. Each organism is discussed with regard to geographic distribution, habitat in the host, morphology, life history, pathogenicity and diagnosis of infection. Tabulated summaries of important facts are given at the end of each section. The illustrations are adequate. The diagrammatic life histories, of which there are 22, should be useful. Practicality is the keynote of the book. It affords a working knowledge of the subject, and is one of the best, if not the best, of its type that has come to the attention of the Reviewer. H. R.

HABITS, THEIR MAKING AND UNMAKING. By KNIGHT DUNLAP, Professor of Experimental Psychology in the Johns Hopkins University. Pp. 326. New York: Liveright, Inc., 1932. Price, $3.00.

MATERIAL in this work is divided roughly into two sections. The first portion presents the fundamental principles, the theories, the process and conditions of efficient learning. It is very interesting and easy reading and is presented largely from the viewpoint of the laboratory psychologist.

The second section attempts to correlate the earlier material with the breaking of specific bad habits. Bad habits such as stammering, masturbation, tics and homosexuality and other reactions supposedly of psychological origin are used as examples in demonstrating how the breaking of such habits may be carried out through a process of "negative practice," or "unlearning," in other words, a so-called reversal of the learning process.

The author's viewpoint is quite unique and certainly very extreme, and cannot be said to be fundamentally sound; for the detailed discussion of the technique of treatment and associated material does not indicate an unprejudiced knowledge of the deep motivations known to be back of such characteristics or habits. The chapter on the breaking of specific bad habits is particularly full of exaggerations and statements that are not supported by a *wide* "clinical" experience. The great simplification of this work, which is intended for the layman, may be responsible for some of the dogmatic tenor but it does not help an otherwise very novel presentation.

The extensive appendix and bibliography is excellently arranged in direct connection with the material presented in various chapters and can be said to be one of the most valuable portions of the book. L. S.

EXPERIMENTAL ANALYSIS OF DEVELOPMENTS. By BERNHARD DÜRKEN, Professor in the University of Breslau. Translated by H. G. and A. M. NEWTH. Pp. 288; 120 illustrations. New York: W. W. Norton & Co., 1932. Price, $4.75.

THE problems and methods of experimental embryology, and some of the results achieved, are here brought together in the form of a survey.

The experimental method in the study of development was used as early as the 18th century, but its modern phase dates from Wilhelm Roux (1850–1924). The material is mostly from the lower vertebrates, especially the amphibians, and from the invertebrates. The subject matter is considered under 8 chapters, such as fertilization and the stimulus to development, the problem of determination, and the influence of environment on the process of development. The number of problems which have already been studied in this comparatively new field is impressive. The details of these are of the greatest interest to the experimentalist and embryologist, but the results and the principles involved have a much wider appeal.

W. A.

BOOKS RECEIVED.

NEW BOOKS.

A Text-book of Neuropathology. By ARTHUR WEIL, M.D., Associate Professor of Neuropathology, Northwestern University Medical School, Chicago. Pp. 335; 260 illustrations. Philadelphia: Lea & Febiger, 1933. Price, $5.00.

Urine and Urinalysis. By LOUIS GERSHENFELD, PH.M., B.Sc., P.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Pp. 272; 36 illustrations. Philadelphia: Lea & Febiger, 1933. Price, $2.75.

Les Rythmes et la Vie. By MM. LAIGNEL-LAVASTINE, A. M. CHANOZ, J. MONCHANIN, G. RICHARD, J. GUITTON, F. MENTRE, H. DUPRAT, H. CARDOT and R. BIOT. Pp. 264. Lyon: Librairie Lavandier, n.d. Price, 15 fr.

Le Nystagmus Vestibulaire et les Réactions de Mouvements. By R. CLAOUÉ, Professeur libre d'oto-rhino-laryngologie (Bordeaux). Pp. 64; 17 illustrations, 2 in color. Paris: Norbert Maloine, 1933.

Cervico-vaginitis of Gonococcal Origin in Children. Report of a Project of The Bellevue-Yorkville Health Demonstration of New York City. By WALTER M. BRUNET, M.D., DORA M. TOLLE, M.D., SARA ALICIA SCUDDER, and ANNE RUTH MEDCALF. Foreword by EMILY D. BARRINGER, M.D., ROBERT L. DICKINSON, M.D., and WILLIAM H. PARK, M.D. Pp. 97; 11 figures, 11 tables and 1 colored plate. New York: Milbank Memorial Fund, 1933.

El Primer Centenar de Enfermos de Lepra Curados por el Dr. A. Benchetrit. Pp. 144; 100 illustrations. Bogotá: Editorial Minerva, 1933.

The Vitamins in Health and Disease. By BARNETT SURE, PH.D., Professor of Agricultural Chemistry, University of Arkansas, Fayetteville. Pp. 206; 4 tables. Baltimore: The Williams & Wilkins Company, 1933. Price, $2.00.

Fighting Disease With Drugs. The Story of Pharmacy. A Symposium. Edited by JOHN C. KRANTZ, JR., with an Introduction by DR. JAMES H. BEAL. Pp. 230; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, $2.00.

Collected Reprints from the Laboratories of the Mount Sinai Hospital, New York, 1932. LOUIS GROSS, M.D., Director.

Ursachen und Behandlung der Krankheiten (causae et curae). By the Aebtissin Hildegard von Bingen. Translated by PROFESSOR DR. HUGO SCHULZ, Greifswald. Pp. 235. München: Verlag der Aerztlichen Rundschau Otto Gmelin, 1933. Price: Paper, Mk. 10.80; Bound, Mk. 13.

Studies in the History of Ophthalmology in England Prior to the Year 1800. By R. RUTSON JAMES, F.R.C.S. (ENG.), Consulting Ophthalmic Surgeon to St. George's Hospital and Senior Editor of the British Journal of Ophthalmology. Pp. 255; 9 plates. New York: The Macmillan Company, 1933. Price, $4.00.

Diet in Sinus Infections and Colds. By EGON V. ULLMANN, M.D., Formerly Special Lecturer for Biology at the Oregon State College; Instructor at the First Medical Clinic at the University of Vienna, etc. Recipes and Menus by ELIZA MEZ. Pp. 166. New York: The Macmillan Company, 1933. Price, $2.00.

Medicine in Canada. Vol. IX of Clio Medica. By WILLIAM B. HOWELL, M.D., Anesthetist-in-Charge, Royal Victoria Hospital; Lecturer in Anesthesia, McGill University, Montreal. Pp. 137; 6 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, $1.50.

El Asma Y Otras Enfermedades Alergicas. By DR. CARLOS JIMENEZ DIAZ. Pp. 945; 88 illustrations, some colored. Madrid: Editorial España, 1932. Price, 60 pesetas.

The Biochemistry of Medicine. By A. T. CAMERON, M.A., D.Sc., F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital, and C. R. GILMOUR, M.D., C.M., F.R.C.P. (C.), Professor of Medicine and Clinical Medicine, University of Manitoba; Physician, Winnipeg General Hospital. Pp. 506; 31 illustrations. Baltimore: William Wood & Co., 1933. Price, $7.25.

International Clinics. Vol. II, Forty-third Series, 1933. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with the collaboration of various contributors. Pp. 314; 31 illustrations, 1 colored. Philadelphia: J. B. Lippincott Company, 1933.

Hyperinsulinism, Pulmonary Hypertension, Stenosis of the Coronary Arteries, the Pathological Physiology of the Circulation, Hypertension, Abnormal Uterine Bleeding, Lymphogranuloma, Standards in Therapeutics, and Recent Progress in Obstetrics and Pediatrics are the subjects discussed in this interesting number.

The Clinical Aspect of Chronic Poisoning by Aluminum and Its Alloys. By LEO SPIRA, M.D., with a Foreword by PROFESSOR DR. HANS HORST MEYER, University of Vienna. Pp. 28; 1 illustration. London: John Bale Sons & Danielsson, Ltd., 1933. Price, 2/6.

Causal Factors in Tuberculosis. A Report of an Investigation into the Incidence of Tuberculosis in Certain Tyneside Districts. By F. C. S. BRADBURY, M.D., D.P.H., Medical Commissioner of Tyneside Inquiry. Pp. 126; various tables. London: National Association for the Prevention of Tuberculosis, 1933. Price, 2/–.

The Medical Clinics of North America, Vol. 16, No. 6 (Mayo Clinic Number, May, 1933). Index Number. Pp. 239; 28 illustrations. Philadelphia: W. B. Saunders Company, 1933.

A Laboratory Manual of Neuro-anatomy. Part II. Stereographic Plates. By C. L. DAVIS, M.D., Professor of Anatomy, University of Maryland, and H. S. RUBINSTEIN, B.S., M.D., Instructor in Neuro-anatomy and Assistant in Medicine, University of Maryland. Baltimore: William Wood & Co., 1933. Price, $3.00.

"This series of stereograms was originally made for use in the teaching of neuro-anatomy at the University of Maryland Medical School. They represent an effort to provide the student at a minimum expense with a satisfactory substitute for the actual specimen. It is designed as an aid to laboratory study of the brain and for bringing to the study an adequate substitute for the specimens usually obtainable in the laboratory alone. Many structures which lend themselves to this method of demonstration are lacking, not because of greater importance of the structures shown but because, in limiting the scope of the work to a point which brings it within the reach of most students, certain structures were arbitrarily selected for demonstration and others omitted." (From authors' Introduction.) Part I, the book itself, will not be ready for publication for a considerable time.

The Heroic Age of Science. The Conception, Ideals, and Methods of Science Among the Ancient Greeks. By WILLIAM ARTHUR HEIDEL, Research Professor of the Greek Language and Literature in Wesleyan University; Research Associate of the American Council of Learned Societies of the Carnegie Institution of Washington. Pp. 203. Baltimore: The Williams & Wilkins Company, 1933, for Carnegie Institution of Washington. Price, $2.50.

A German Doctor at the Front (*Die Front der Arzte*). By PROFESSOR DR. WILHELM HIS. Translated from the Original German by COLONEL GUSTAVUS M. BLECH, Medical Corps, Reserve, and BRIGADIER-GENERAL JEFFERSON R. KEAN, Medical Corps, U. S. A. (Retired). Pp. 230; 1 illustration. Washington, D. C.: The National Publishing Company, 1933 (American Edition). Price, $2.50.

Modern Aspects of Gastro-enterology. By M. A. ARAFA, M.R.C.P. (LOND.), Medical Assistant to Guy's Hospital, London; Medical Tutor to the Egyptian University and Formerly Senior Medical Registrar to Kasr-el-ainy Hospital, Cairo. With a Foreword by ARTHUR F. HURST, M.D., F.R.C.P., Senior Physician, Guy's Hospital, London. Pp. 374; 79 illustrations. Baltimore: William Wood & Co., 1933. Price, $8.25.

Filterable Virus Diseases in Man. By JOSEPH FINE, M.D., B.Sc., D.P.H. (GLAS.), D.T.M. (LIVERPOOL), Assistant to the Professor of Public Health, Edinburgh University; Formerly Research Assistant, Sir Alfred L. Jones Laboratory (Liverpool School of Tropical Medicine), Freetown, Sierra Leone; Late Assistant Pathologist, Ancoats Hospital, Manchester. Pp. 144. Baltimore: William Wood & Co., 1932. Price, $2.25.

NEW EDITIONS.

Surgical Pathology. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), Dipl. Psych., F.R.C.S., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Pp. 866; 477 illustrations and 13 colored plates. Third edition thoroughly revised. Philadelphia: W. B. Saunders Company, 1933. Price, $10.00.

This edition retains the excellences of former editions and this is intended as high praise. In addition to extensive alterations, new sections have been added on: metabolism of tumors, the goitrigenous action of cabbage, chronic follicular gastritis, developmental enterogenous cysts, lesions of the appendices epiploicæ, Masson's musculonervous complex of the appendix, autolytic peritonitis, cholecystitis glandularis proliferans, high temperature deaths following cholecystectomy, obstruction of the common bile duct, non-obstructive hydronephrosis, injuries to the spleen, bloody discharge from the nipple, Cushing's syndrome, cysts of the semilunar cartilages, and the absorption of bone.

A Dictionary of Greek and Latin Combining Forms Used in Zoölogical Names. By EDMUND C. JAEGER, Head of the Department of Zoölogy, Riverside Junior College, Riverside, California. Pp. 157. Second edition. Springfield, Ill.: Charles C Thomas, 1931. Price, $1.50.

The Art of Marriage. A Scientific Treatise. By J. F. HAYDEN, B.Sc. Pp. 218. Revised and enlarged edition. High Point, N. C. Book Sales Agency, 1931. Sales agent: The Union Library Association, New York. Price, 98 cents.

There is no question but that these topics like those of birth control should be available to the intelligent public.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Heart After Diphtheria.—The well known tendency for occasional involvement of the heart muscle and rare implication of the conduction system during the course of acute diphtheria has raised important questions in reference to this disease causing permanent heart damage. The first serious effort to make a study of the post-diphtheritic heart was made by White and Smith in 1905. Their cases were examined, however, only a comparatively few months after the patients were convalescent from diphtheria. Hoskin has also made an electrocardiographic examination in patients convalescing from the disease, while Jones and White 6 years ago examined 100 patients who had had diphtheria from 5 to 8 years previously. They could find no evidence of organic heart disease in patients who had had diphtheria with that length of time intervening. Sutherland agrees that diphtheria does not have a lasting effect on the heart, whereas Rolleston thinks that it does produce injury and Butler and Levine hold the same view in the instance of heart block. STANLEY ALSTEAD (*Lancet*, 1933, **224**, 413) has reinvestigated the whole subject, studying a large number of children who have had diphtheria 1 to 10 years prior to the time of the examination. A considerable number of the cases were excluded for various reasons which might be instrumental in bringing heart changes as a result of some condition other than diphtheria. Ultimately 150 cases were selected for study. The average age of this group was 14 years. There were 21 (14 per cent) who had a history of clinical abnormalities in the heart during diphtheria. Only 2 of these had any symptoms or signs of cardiac lesion on reëxamination. Eight patients presented signs and symptoms suggestive of cardiac abnormalities but 2 of these cases were subsequently omitted because the cardiac abnormality was of doubtful importance. In reviewing the brief case reports of these 8 cases it seems that there are 2 or 3 others which might well have been omitted, but aside from that, accepting the author's diagnosis, only 3.3 per cent of the series showed clinical evidence of heart abnormality and, of these, only 2 showed abnormal electrocardiograms. In the group as a whole, the electrocardiograms as contrasted with 100 control cases were virtually the same if such differences as occurred are considered to be caused by chance factors. The only exception to this was that in 90 of the cases of diphtheria there was a negative or isoelectric *T* wave, which abnormality may

or may not mean very much and is of doubtful pathologic significance. The *P–R* interval was remarkably constant. In only 4 instances was there any example of delayed conduction. The *Q–R–S* complex showed a complete absence of any evidence of intraventricular block. The author concludes that "there is nothing to suggest the occurrence of gross cardiac lesions as a result of previous attacks of diphtheria," although he does point out that the abnormalities of the *T* wave in Lead III which are so common in active diphtheria have a tendency to persist long after the disease has subsided.

SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.,

J. WILLIAM WHITE PROFESSOR OF SURGICAL RESEARCH, UNIVERSITY OF PENNSYLVANIA,

AND

C. G. JOHNSTON, M.S., M.D.,

INSTRUCTOR IN SURGERY, UNIVERSITY OF PENNSYLVANIA,

PHILADELPHIA, PA.

Duodenal Drainage in Gall Bladder Disease.—About a decade ago there appeared a large number of papers dealing with the use of duodenal drainage in the diagnosis and treatment of disorders of the biliary tract. The interest in this subject was not prompted by new discoveries, but rather by the enthusiasm of individuals who attempted to correlate physiologic principles and clinical methods with diseases of the bile passages. The chief exponent of duodenal drainage for the diagnosis and treatment of disorders of the biliary tract was LYON (*Am. J. Med. Sci.*, 1920, **160**, 515), who believed that by the application of the theory of MELTZER (*Ibid.*, 1917, **153**, 469) concerning the contrary innervation of the gall bladder, and the sphincter of Gage and Oddi, the gall bladder could be made to empty its contents into the duodenum and that he could collect fractionated specimens of bile from the duodenum. From an examination of these bile fractions Lyon thought that he could differentiate various conditions of the gall bladder and by repeatedly draining the bile from the diseased gall bladder could restore that organ to its normal state. He not only felt that by this method he could determine the presence or absence of pathologic lesions of the biliary tract, but could localize the portion of the tract involved by the mucosal cells found in the material removed from the duodenum.

The objections which arose following Lyon's paper are too voluminous to include in a review. Suffice it to say that these objections dealt chiefly with the ability to cause emptying of the gall bladder, and even if the gall bladder could be made to empty, with the identification of the gall bladder fraction as such. In regard to treatment by duodenal drainage, those opposed to Lyon's method did not believe that it could bring about improvement in the presence of stones or in a viscus whose walls were infected. Unbounded enthusiasm on one hand and extreme skepticism on the other made it difficult to evaluate the

method. In 1924, JONES (*Arch. Int. Med.*, 1924, **34**, 60) summarized the controversy thus: "Unquestionably, the early, rather extravagant claims for the method, as a means of diagnosis and treatment, have not been fulfilled. It is also unfortunately true that much of the criticism and pessimism with which the subject is now viewed is due to the claims that have been made by some enthusiasts as regards the efficacy of treatment by duodenal drainage. The undoubted psychologic effect produced by such treatment has undoubtedly been overlooked, or not mentioned by many. On the other hand, the somewhat unequivocal stand of Alvarez and other authors, that the method is without any value, seems equally unjustifiable."

When GRAHAM and COLE (*J. Am. Med. Assn.*, 1924, **82**, 613) presented cholecystography as a means of determining the functional state of the gall bladder the question as to the efficacy of duodenal drainage was in doubt and the method was used routinely in but few clinics throughout the country. With the advent of cholecystography other tests for the diagnosis of disorders of the gall bladder became overshadowed. However, in spite of the widespread favorable results with the Graham-Cole test, there were those who, while not agreeing completely with Lyon, felt that the use of duodenal drainage had merit as a diagnostic test. LYON (*Am. J. Med. Sci.*, 1920, **160**, 515) depended upon the color and consistency of the gall bladder fraction, the reaction, the microscopic appearance of the cellular débris, and the ease with which this dark fraction could be obtained, for his interpretation of the state of the gall bladder and bile ducts.

JONES (*Arch. Int. Med.*, 1924, **34**, 60) and PIERSOL, BOCKUS and SHAY (*Am. J. Med. Sci.*, 1928, **175**, 84) stated that a study of the sediment obtained after drainage was of the greatest diagnostic import, especially the finding of cholesterol or so-called calcium bilirubinate crystals. During the past year ROUSSELOT and BAUMAN (*J. Am. Med. Assn.*, 1933, **100**, 254) and RAFSKY (*Am. J. Med. Sci.*, 1933, **185**, 851) have published papers which emphasize anew the advantages of a study of this sediment in the diagnosis of cholelithiasis.

Whether or not the incidence of accurate diagnoses will be higher from a study of the crystallography of the bile obtained from duodenal drainage than from the more commonly used method of GRAHAM and COLE (*J. Am. Med. Assn.*, 1924, **82**, 613) cannot be answered from a small series of cases presented from a few clinics. Either method of study requires skill not only in obtaining the necessary data, but in the interpretation of the findings. PIERSOL, BOCKUS and SHAY (*Am. J. Med. Sci.*, 1928, **175**, 84), in comparing the two methods, reported correct diagnoses in 88 per cent of cases by means of duodenal drainage as compared with 65 per cent with oral cholecystography. Their results from duodenal drainage are very commendable, but the results from cholecystography seem low. Later, BOCKUS, SHAY, WILLARD and PESSEL (*J. Am. Med. Assn.*, 1931, **96**, 311) in an additional study reported that in their hands duodenal drainage gave 98 per cent correct results as compared with 88.4 per cent by cholecystography. However, it appears that with individuals less skilled in duodenal drainage, cholecystography is still the method of choice for the diagnosis of gall bladder disorders.

Since much of the confusion concerning the place of duodenal drainage in the diagnosis of gall bladder disease has resulted from loose

terminology and much theorizing, the use of the term "calcium bilirubinate crystals" for the material which the adherents of the duodenal drainage method believe is characteristic of cholelithiasis is unfortunate, in that it suggests that the identity of the material is as well known as is the entity spoken of as "cholesterol crystals." The fact that this material is colored might suggest the presence of bilirubin, but there is no very plausible reason for stating definitely that the material is the calcium salt of bilirubin.

THERAPEUTICS

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The Treatment of Eclampsia and Pre-eclampsia With Thyroxin.—KÜSTNER (*Klin. Wchnschr.*, 1932, **11**, 1016) and others claim that in eclampsia there is an increased activity of the hypophysis, with an increased production of posterior lobe hormone. Although evidence is available that thyroid function is also increased, as a result of the overactivity and antagonistic effect of the posterior lobe pituitary hormone, the balance is dominated by the latter. This concept suggests that the use of thyroxin in eclampsia is rational. The author administered thyroxin in 48 cases of eclampsia. The daily dose varied usually between 2 and 3 mg. by mouth. The total amount administered also showed considerable variations. One patient received 8 mg.; another, 48 mg. In 26 cases, the author claims an improvement due to thyroxin. The improvement manifested itself either in the cessation of convulsions or in decrease of the edema. In 18 cases the improvement was not definite. One patient died. None of the cases with marked improvement had an arterial pressure over 180 mm. Hg systolic pressure; but the edema in this group was usually of marked degree. The group with no improvement, on the other hand, exhibited a relatively higher systolic arterial pressure (180 to 230 mm. Hg) and slight edema only. Cases with pre-eclamptic manifestations showed particularly marked improvement. The author does not advocate thyroxin therapy alone, but states that in some cases it may be of great benefit. Even relatively large doses of thyroxin failed to exert obvious harmful effects on the mother or on the fetus.

Clinical Experiences With Glucose-insulin Treatment of Cardiac Disease.—Following the introduction of the therapeutic administration of glucose by Büdigen as a valuable addition to the usual methods of the treatment of cardiac failure, there has more recently been recommended a modification of his plan of therapy in which from 30 to 50 gm. of glucose are given orally or intravenously in the morning fasting state and are followed in from 15 to 20 minutes by a subcu-

taneous dose of 10 to 30 units of insulin. In view of the fact that insulin has been proved to exert harmful effects in the presence of the diseased heart, possibly because of its effect upon glycogen metabolism in the heart, LASCH (*Med. Klin.*, 1932, **28**, 1675) studied this procedure in 12 patients suffering from the severest grade of chronic cardiac insufficiency. All 12 were subjected to thoroughly controlled observations which were continued over a considerable length of time. After their response to the prolonged administration of salt-poor diet, digitalis and salyrgan there was added without alteration in their previous treatment the daily administration for 10 days of 50 gm. of grape sugar administered orally and followed after 15 minutes by 10 units of insulin. The author was unable to find any evidence that this addition of sugar and insulin was in any way beneficial to the patient or altered his response to the previous treatment. In some of the cases, moreover, the patient's condition was actually less favorable following than before the administration of the sugar and insulin. The author concludes that this form of therapy for the decompensated cardiac patient is not only valueless but may actually be harmful. He specifically states, however, that this is not to be construed as reflecting upon the therapeutic value of the intravenous use of glucose without insulin.

Bichlorid of Mercury Inhalations in the Treatment of Gangrene of the Lung.—ENGEL (*Deutsch. med. Wchnschr.*, 1932, **58**, 1924), having obtained such very satisfactory results from its employment along with other methods in the treatment of gangrene of the lung, seeks to reintroduce the use of inhalations of a vapor of a 1 to 1000 solution of corrosive sublimate. He reports 12 patients so treated in the last few years of whom 4 died, 3 were significantly improved and 5 completely cured. He administers these sublimate inhalations 2 or 3 times daily, spraying in the form of steam a dose of 25 cc. of the solution at each application. He has never seen any unpleasant or harmful effects in spite of sometimes having continued this treatment for 5 or 6 weeks, and there has never been any evidence of mercurial poisoning. He warns that on account of mild irritative conjunctivitis the eyes should be protected from the sublimate spray. The beneficial effects of the treatment usually begin promptly and are first seen in a diminution or disappearance of the putrid odor of the sputum and breath. This is followed by diminution in the amount of sputum and a fall in the temperature. Since the value of arsphenamin and of myrtol are so well established, he combines the administration of these agents with the use of sublimate spray.

Work and Insulin in the Management of Diabetic Patients.—It is established that in milder cases of diabetes moderate or severe muscular exercise usually acts beneficially; the blood sugar falls and the glycosuria may even disappear. In severe cases, on the other hand, there may follow an increased blood sugar content and glycosuria, and acetone bodies may appear. BRAUCH (*Deutsch. Arch. f. klin. Med.*, 1932, **174**, 352) reinvestigated this problem with reference to the usual occupational work of the patient and to insulin dosage. For this purpose a comparison was made of the patients' behavior while performing their

usual work in the morning and while resting. These tests were repeated in some of the cases 2 months after the dietetic-insulin-work régime was established. In every case the arrangement followed has considered the individual occupation and character of the diabetes. The response of the patients to muscular work was not uniform. In 3 patients the occupational work resulted in a marked lowering of the blood sugar and urinary sugar elimination. In 7 patients a similar response was observed after moderate work. In 2 patients no difference was noted while at rest or while working. In 1 severe case the work resulted in an aggravation of the condition. The author emphasizes the value of individual gauging of work, diet and insulin.

PEDIATRICS

UNDER THE CHARGE OF
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Raw Basic Feeding in the Prevention and Treatment of Dental Caries.—KUGELMASS and KING (*Arch. Pediat.*, 1933, **50**, 307) state that dental caries is a syndrome of many systemic and local disturbances rather than a simple disease of single etiology. Determination of the degree of dental caries was made by means of Bodecker's life caries index in children under continuous supervision for other systemic conditions. Children free from dental caries were of the more stable elements of their race, whose general and mouth hygiene were superior to children with marked dental caries. Dental caries is at its maximum at 6 years for deciduous teeth and at 12 years for permanent teeth, the incidence increasing rapidly with age. This rhythm parallels that of development, thus relating dental caries to deep-seated metabolic changes in the growing body. The degree and prevalence of dental caries was not affected by recurrent mouth and upper respiratory infections. Dental caries is neither prevented nor minimized by breast feeding. Children free from dental caries were maintained in infancy on base-forming dietaries containing early additions of semisolid feeding in the first months of life. Children with moderate and extreme dental caries showed inadequate intakes of vitamins B, C and D. Those maintained on ketogenic diets, base-forming in their mineral content, showed marked dental caries. Those free from dental caries showed consistently a dietary intake excessive in alkali-forming minerals with a preponderance of raw fruits and vegetables. Races immune to dental caries consume sufficient raw alkali-forming fruits and vegetables to balance the acid-forming fresh fish and raw meat.

The Relationship of the Rheumatic Process to the Development of Alterations in Tissues.—COBURN (*Am. J. Dis. Child.*, 1933, **45**, 933) says that when the rheumatic subject is infected with the hemolytic streptococcus, the initial response is of the usual character. If the infection is limited to the upper respiratory tract, recovery follows in the course of a few days. This illness, although mild, may be the first

phase in the development of a severe rheumatic attack. Following the subsidence of the local infection, the patient usually regains his usual health, and nothing abnormal is detected clinically. This quiescent stage of days or a few weeks represents the second phase in the evolution of the rheumatic process. This second phase persists until there is a response in the production of immune bodies in the peripheral circulation, whereupon the rheumatic process is activated in susceptible persons. When this occurs, the initial response is characterized by manifestations of a hemorrhagic nature. The most frequent are epistaxis and the erythemas. Melena, hemoptysis and hematemesis also occur. Studies of the excretion of erythrocytes in the urine indicate that there is a very close relationship of hemorrhage to the rheumatic process. Late in the attack, when symptoms are subsiding and abnormal urinary manifestations have disappeared, there may be a second stage, characterized clinically perhaps only by the appearance of subcutaneous nodules. When it was possible to study the tissues of patients dying during the initial stage of a rheumatic attack, hemorrhagic lesions without distinctive histologic character were conspicuous. The appearance of these non-specific lesions suggested the activity of a single process with varying degrees of intensity. This varied from engorgement of the bloodvessels; alteration of the permeability of the vascular tissues with diapedesis, but without demonstrable change in the structure, to inflammatory reaction. The damage to the tissue in the patients with acute rheumatism was characterized by the absence of detectable microörganisms and commonly by vasodilatation, swelling of the endothelium, necrosis of the collagen, infiltration with various wandering cells, and especially hemorrhage. During the first cycle of the rheumatic attack, few or no Aschoff bodies were detected in the cardiac muscle, but the diagnosis was established by the presence of the specific lesions in the endocardium. In this group most of the rheumatic subjects who died survived a long illness with rheumatic fever. In these patients hemorrhage was not conspicuous, and numerous Aschoff bodies were found in the heart muscle. The constant proximity of the Aschoff cells to necrotic collagen in these myocardial nodules suggest the process of healing. The evolution of rheumatic fever consists of three phases. In most instances recognition of the condition clinically is not established until the development of the third phase.

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Studies in Cretinism and Hypothyroidism: Blood Cholesterol.—BRONSTEIN (*J. Am. Med. Assn.*, 1933, **100**, 1661) undertook this study in order to establish an additional method for regulating thyroid therapy, and so that the clinical course of the thyroid-deficient child might be better understood. It has been shown previously in adults that a relationship existed between hypercholesteremia and hypothyroidism. It was attempted to show that a similar relationship existed in childhood. The blood cholesterol was determined in 25 children in whom no known derangement of cholesterol metabolism was present, and the average was found to be 190+. This value for cholesterol is substantiated by the results of other investigators in this field. Hypercholesteremia was found in the 12 thyroid-deficient children studied. The values ranged from 277 to 782. Thyroid therapy definitely lowered

the blood cholesterol in the cases cited, in addition to raising the basal metabolic rate and effecting clinical improvement. It is desirable to have an additional method for the diagnosing and treating of thyroid-deficient children, particularly in infants and in borderline cases. The use of cholesterol as an aid in the diagnosis and the regulation of therapy offers very satisfactory and definite possibilities.

DERMATOLOGY AND SYPHILIS

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Bacteriologic Studies on Lichen Planus.—In a disease whose etiology has occasioned much speculation, JACOB and HELMBOLD (*Arch. Dermat. and Syph.*, 1933, **27**, 472) present significant evidence for a specific organismal cause. These authors have isolated a Gram-negative, anaërobic, non-motile, non-spore-bearing bacillus from excised lesions in 25 of 28 cases of lichen planus studied. The organism, though somewhat polymorphic, resembles organisms of the colon typhoid type but cannot as yet be definitely classified because of its relatively poor growth. Semisolid dextrose serum agar containing cubes of human tissue was the medium used. The serum must be inactivated at from 56° to 60° C. for a number of hours. The organism was not found in normal skin nor in a number of cases of other papular diseases used as controls. Inoculation of human skin with the organism isolated in a few instances produced lesions which both clinically and histologically resembled lichen planus.

Postoperative Gangrenous Ulcer of the Abdominal Wall.—Increasing interest has been shown in the occasional development of postoperative gangrenous ulcers usually following septic operations on the abdominal cavity, generally in men, and DUEMLING and ELSTON (*Arch. Dermat. and Syph.*, 1933, **27**, 624) give an excellent review of the literature, discuss the clinical features, and report an additional case following operation for a ruptured gastric ulcer, with new suggestions for treatment. While authorities vary as to the causative organism, the consensus of opinion points to a streptococcus and a staphylococcus which invades the tissues in symbiotic relationship. This type of progressive gangrenous ulceration usually develops about a drainage opening or stitch hole from 7 to 21 days postoperatively. Most cases follow operations on the gall bladder or intestinal tract in men, rare examples in women even after operation for pelvic inflammatory disease being on record, however. The condition begins as a small, painful, purplish papule which breaks down, ulcerates and spreads in a serpiginous

manner, involving skin, subcutaneous tissue and fascia. In the absence of effective treatment, the process will involve the entire abdominal wall within a period of a few weeks. The authors advocate the use of the infiltration of skin and subcutaneous tissue in advance of the gangrenous process with 5 cc. of bacteriophage (staphylococcus and colon bacillus). This was followed by a general reaction with chill and elevation of temperature to 103° F. in the patient under observation, but repetition of the infiltration at a 5-day interval for 3 times resulted in less systemic reaction and prevented further extension of the process. The authors also recommend the use of oxyquinolin sulphate and scarlet red impregnated gauze originally advocated by Bettman as an epithelial stimulant and for relief from pain attendant on changing dressings.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Friedman Pregnancy Test.—Since the introduction of the Aschheim-Zondek biologic test for pregnancy, there has been considerable interest in work of this sort because of the very high percentage of accuracy. The modification of the test devised by Friedman, in which rabbits are used instead of mice, has been accepted by many investigators on account of certain economic and practical advantages. According to McNeile and Reynolds (*Calif. and West. Med.*, 1933, **38**, 1) the Friedman test has an accuracy of about 98 per cent, which parallels that of the Aschheim-Zondek test. It is as yet uncertain as to exactly how soon after conception the reaction becomes positive, probably not under 3 weeks, so that early pregnancy, if negative, should be checked a second time 7 to 10 days later. The test determines the presence of live placental tissue or tissue of placental origin in contact with the maternal circulation. It may, therefore, give false positives in the presence of missed abortions, incomplete abortions or ectopic pregnancies with dead fetal tissue. The reaction might be positive in the case of a macerated fetus as the placenta in these cases frequently contains live tissue. The test is strongly positive in the presence of hydatid mole and chorionepithelioma, and quantitative Aschheim-Zondek tests become an important aid in the diagnosis, treatment and prognosis of these conditions. Primary ovarian failure or castration may cause a compensatory hypertrophy of the anterior lobe of the pituitary gland which may throw an excess of its hormone into the circulation, thus accounting for a certain number of false positive reactions. The technique which they suggest is the injection of 7 cc. of fresh urine on 2 successive days, using a controlled rabbit over 12 weeks of age, killing the animal at 48 hours.

OPHTHALMOLOGY

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Ocular Syphilis.—III. Review of the Literature and Report of a Case of Acute Syphilitic Meningitis and Meningoencephalitis with Special Reference to Papilledema. DRAKE (*Arch. Ophthal.*, 1933, **9**, 234) reports a case of acute syphilitic meningitis and meningoencephalitis in which bilateral choked disks with concentric contraction of the visual fields and limitation of external and downward rotation of the left eye were prominent symptoms. The patient also had occipital headaches, rigidity of the neck, nausea and vomiting, left facial weakness and sluggish pupillary reactions. The Wassermann reactions of both blood and spinal fluid were strongly positive. The spinal fluid contained 227 lymphocytes per cubic millimeter. Under intensive antiluetic treatment, the edema of the disks receded promptly and had completely disappeared in about four months. The vision was considerably improved. Although some authorities believe that acute syphilitic meningitis is always a neurorecidive, only 11 of the 50 cases found in the literature by the authors had had previous antisyphilitic therapy. Of the 30 cases in which examination of the ocular fundus was recorded, 8 showed papillitis, 14 bilateral papilledema, and 2 unilateral papilledema. Argyll-Robertson pupils were present in 7 cases. The Wassermann reaction of the blood was strongly positive in 45 of 48 cases. The Wassermann reaction of the spinal fluid was strongly positive in 49 of the 50 cases. The average cellular content of the spinal fluid was 414 cells per cubic millimeter. The majority of the cells were lymphocytes. Papilledema of syphilitic origin is almost invariably a symptom of acute syphilitic meningitis or meningoencephalitis, which may occur during the secondary stage or more rarely as an acute exacerbation in congenital syphilis, or in a latent period of the tertiary stage. Associated symptoms are headache, nausea and vomiting, coma, delirium or some other mental disturbance, and involvement of other cranial nerves, especially the 3d, 6th, 7th and 8th. The Wassermann reaction of the blood is positive in about 90 per cent of cases, and that of the spinal fluid is always positive. The cerebrospinal fluid is always under increased pressure and contains an increased number of cells. If the Wassermann reaction of the spinal fluid is negative on several successive examinations, the diagnosis of acute syphilitic meningitis is not justified. The prognosis is usually good if antisyphilitic treatment is started promptly. The papilledema usually responds very well to antisyphilitic treatment, but in some cases is followed by postneuritic atrophy. Histologically, acute syphilitic meningitis is characterized primarily by a diffuse, small cell infiltration of the piaärachnoid in which lymphocytes predominate. The infiltration occurs especially around the bloodvessels and extends along them into the brain tissue. The region of the chiasm is often involved in the meningitic process, and the cranial nerves, especially the optic and auditory, are often markedly infiltrated with lymphocytes and plasma cells.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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The Relationship of Upper Respiratory and Alimentary Tract Flora to Mastoid Infections, With Particular Reference to the Epidemiology of Mastoiditis.—Wisely employing Holman's method for differentiating and classifying streptococci, KOPETZKY and HADJOPOULOS (*Laryngoscope*, 1933, **42**, 661) correlate the bacteriologic findings of cultures made from otitic suppurative lesions with their analyses of certain statistics collected from the records of a general hospital during the sexennium 1926–1931. From an epidemiologic standpoint, it was found that approximately 3 per cent of the total hospital admissions were otologic cases, which seemed to increase in number triennially. The incidence of acute otitic infections reached the peak in March and April; whereas the greatest number of chronic cases occurred in August and September. The mortality curve virtually paralleled that of the chronic infections, and was highest when the general incidence was lowest. The authors believe their studies confirm a phenomenon common to all epidemics—namely, towards the end of the epidemic the ratio of mortality to morbidity shifts in favor of mortality. The general mortality rate was somewhat over 5 per cent, ranging between 8.6 per cent in 1930 and 2.3 per cent in 1931. Unable to explain this fluctuation satisfactorily by data at hand or by merely differentiating the streptococci (which were by far the commonest microörganisms encountered) into the three major groups—hemolytic, green and indifferent—the authors proceeded more minutely to analyze their bacteriologic data. The bacteriologic technique for differentiation and classification of the streptococci was that of Holman, although from the authors' description one gets the impression that the individual strains were not isolated in pure culture before being introduced into the differential fermentation "sets." Moreover, pneumococcus, Type III, is classified as a streptococcus. Hemolytic streptococci were found to be the infecting microbe in about 90 per cent of all cases. S. pyogenes accounted for 80 per cent of the cases dying from mastoiditis. S. infrequens was associated oftenest with chronic mastoiditis. Study of the annual variations of the streptococcic types in mastoiditis revealed an orderly sequential periodicity, suggesting major cyclic recurrences every 5 or 6 years. According to their findings, indifferent streptococci predominated in 1927 and 1929. S. infrequens in 1928, S. pyogenes in 1930, and S. subscidus hemolyticus in 1931. The authors state that "the existence of such a cyclic change in streptococcic types is borne out by the findings for all other metastatic foci as well as otitic infections." A related paper, "The Prognostic Value of Streptococcic Subculture in Affections of the Ear," was published subsequently by Hadjopoulos in *Laryngoscope*, 1932, **42**, 771.

ABSTRACTOR'S NOTE.—Holman's original contribution, "The Classification of Streptococci," appeared in *J. Med. Res.*, 1916, **24**, 377, and was abstracted in AM. J. MED. SCI., 1917, **153**, 427.

RADIOLOGY

UNDER THE CHARGE OF

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d'Arsonvalization in Hyperpiesis. — In the opinion of HUMPHRIS (*Arch. Phys. Ther., X-ray, Rad.*, 1932, **13**, 786) the importance of the d'Arsonval current in its ability to lower a high blood pressure can hardly be overestimated. When there is failing ventricular compensation no attempt should be made to lower the peripheral resistance, but these cases are in the minority. In the great majority of cases the increased tension is due to the imperfect elastic recoil in the arterioles (even with arteriosclerosis) plus increased peripheral resistance, and in these cases the d'Arsonval current acts as a safe specific. The author regards it essential to employ apparatus capable of delivering 2500 ma. by the auto-condensation method.

A Roentgen Ray Sign in the Diagnosis of Reducible Esophageal Orifice Hernias.—A roentgenologic sign of reducible hernias at the esophageal orifice is described by CARTY (*Radiology*, 1933, **20**, 174). The patient is examined in the vertical, right anterior oblique position, and the ordinary barium mixture is employed. While the breath is held in full inspiration the patient is told to swallow. At that moment the examiner exerts pressure on the anterior abdominal wall with his hand. If a hernia is present the barium stream usually takes an upward course as it is about to enter the stomach. For obvious reasons roentgenographic depiction is usually impracticable, and the observation is essentially roentgenoscopic.

What Do You Think of Physical Medicine?—SHAULL (*Arch. Phys. Ther., X-Ray, Rad.*, 1933, **14**, 105) points out that it is as difficult to answer this frequently asked question as to answer "What do you think of Radiology?" or "What do you think of internal medicine?" Physical medicine is neither a cult nor a system of healing, and there is no definite line of demarcation between this specialty and surgery or internal medicine. To remove a tumor a surgeon may employ an ordinary scalpel, one heated in a bed of coals, one heated by an electric current, or a cold wire needle with an undamped high frequency current concentrated at its point. In the first two instances the procedures are recognized as surgical; in the last two the operator is perhaps employing physical therapy, although there is no vast difference between any of the methods. In a patient suffering from paresis the internist produces a certain number of temperature elevations by inoculating him with malaria. The physical therapist produces exactly the same number of temperature elevations of exactly the same curve

(if he elects) with diathermy or the hot bath. The results, as far as the paresis is concerned, are quite comparable. It is true that the internist has the malarial parasite and the anemia it has produced to deal with at the end of the series, while the physical therapist has only to turn off his machine or drain his tub. The attempt to evaluate physical medicine as a whole should be abandoned. It is almost as foolish as to attempt to evaluate internal medicine as a whole. In its place the critical evaluation of new appliances and methods of physical therapy by capable men is very badly needed.

NEUROLOGY AND PSYCHIATRY

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Psychologic Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal.—LINDERMANN (*Am. J. Psychiat.*, 1932, **11**, 1083) feels that sodium amytal produces a marked change in the behavior of certain types of psychotic patients and a less pronounced change in the emotional attitudes of normal individuals, on the basis of the release of inhibitions. It allows the study of the thought content of stuporous patients, which was previously not possible and gives material which can be used in psychotherapeutic efforts.

Mental Disorders in Siblings.—HUMM (*Am. J. Psychiat.*, 1932, **12**, 239) presents a study of several hundred individuals in order to determine the relative importance of hereditary and environmental factors in persistent criminalism, manic-depressive psychoses, dementia precox, epilepsy and mental deficiency. The individuals consisted of 858 siblings of patients suffering from mental disorders and 214 pairs of twins, one or both of each pair being affected with a mutual disorder. He found that the closer the degree of genetic relationship to an affected subject, the greater the tendency to mental disorder; that some prenatal factor or factors other than heredity play a part in the causation of mental deficiency; that such factor or factors are more frequently operative in twin than in single births; and that this factor or factors are apparently not operative in the other mental disorders studied. He found also that many siblings were affected with disorders dissimilar to those of their respective prepositi. He found a very frequent familial coëxistence of epilepsy with migrainous headaches, enuresis and outbursts of rage. In a similar way he found a familial association between manic-depressive psychoses and cases of cycloid personality. The incidence of mutual disorder was greater in the males than in the females, although the female ratio is unquestionably greater in manic-depressive psychoses and in mental deficiency.

PATHOLOGY AND BACTERIOLOGY

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Contributions to the Pathologic Physiology of Inflammation: The Action of Histamin on Tissue Metabolism.—Experiments on white mice were carried out by BÜNGELER (*Frankf. Ztschr. f. Path.*, 1932, **44**, 1) to determine whether histamin injected into the living animal or allowed to act directly upon fresh tissue *in vitro* would influence the tissue metabolism as determined by the Warburg method. It was shown that the injection of small amounts of histamin corresponding to about one-tenth of the lethal dose brought about a definite increase in the oxygen consumption of the liver tissue; the greatest increase was observed within an hour of the injection (40 to 50 per cent above the normal O_2 consumption) and fell off to normal within 2 or 3 hours. This type of increased metabolism corresponds to that observed by Hess (*Frankf. Ztschr. f. Path.*, 1931, **42**, 89), following experimentally induced inflammation of the skin. The author, therefore, believes that the elevation of tissue metabolism observed by Hess was due to the liberation of histamin into the blood stream from the foci of inflammation in the skin. He draws attention to the evidence brought forward by other authors purporting to show the appearance of histamin in anaphylaxis and inflammation and concludes FISCHER-WASELS (*Frankf. Ztschr. f. Path.*, 1931, **42**, 1) is correct in his theory that the toxic effects (Fernwirkungen) of inflammation are due in part at least to the liberation of products of protein disintegration, chief of which are histamin and allied substances. The injection of large doses of histamin leads on the other hand to a depression of liver metabolism (if the animal is examined in the stage of severe shock). This change of tissue respiration corresponds to that which the author has shown to occur in anaphylactic shock.

Contributions to the Pathologic Physiology of Inflammation: The Effects of Localized Inflammation on the Reticuloendothelial System as Determined by Vital Staining.—EICHBAUM and SCHEUFLER (*Frankf. Ztschr. f. Path.*, 1932, **44**, 10) produced extensive subcutaneous inflammation in rabbits by injections of silicious dust (Kieselguhr). They then investigated the ability of the reticuloendothelial system to take up vital dyes, and found that the absorption of trypan blue was mildly accelerated about 96 hours after the skin lesions were instigated. With Congo red they found no deviation from the normal. In contrast to the relatively slight effect produced on the reticuloendothelial system by localized inflammation, intravenous injection of milk gave rise to a conspicuous acceleration of the disappearance of Congo red from the blood stream. Subcutaneous injection of milk produced a similar but

more sluggish reaction. Intravenous injection of caseosan markedly accelerated the disappearance of trypan blue from the blood stream, but had no effect on the absorption of Congo red by the reticuloendothelial system. The authors believe that the rapidity with which vital dyes quit the blood stream is proportional to the phagocytic activity of the reticuloendothelial system and feel justified in concluding that this function of the reticuloendothelial system is mildly increased as a result of localized inflammation, though the increase is small compared to that which can be produced by intravenous injections of foreign proteins.

On the Influence of the Vegetative System on the Cholesterin Content of the Blood.—The few observations made (*e. g.*, in cases of anaphylactic shock, pregnancy, dementia precox) on the influence of the autonomous nervous system on the proportion of cholesterin in the blood indicate that vagotony and hypercholesterinemia are associated with each other. GOEBEL (*J. de phys. et de path. gen.*, 1932, **30**, 340) has studied the influence of the vegetative system on the level of cholesterin by pharmacologic methods. He uses a procedure based on the researches of Kraus and Zondek, increasing the quantity of calcium in the organism, and thus causing a temporary displacement of the equilibrium of the electrolytes in the blood in favor of calcium and obtaining excitement of the sympathetic nerve. Dogs were given intravenous administration of 0.2 grains $CaCl_2$ in 20 per cent solution per kg. weight, with determinations of the cholesterin in the blood before and at intervals after the injection. This showed that the raising of the tone of the sympathetic nerve by calcium salts brings about hypocholesterinemia. The predominance of the sympathetic nerve was then brought about by paralysis of the parasympathetic by strong doses of atropin (0.005 to 0.01 grains by kg. weight), and it was observed that within 1 hour after administration a diminution of the proportion of cholesterin in the blood was produced. Experiments were then made to study the behavior of cholesterin in the blood during tonic domination of the pneumogastric nerve. The vagus nerve was stimulated by potassium ions (KCl in 10 per cent solution) and then by paralysis of the sympathetic system with ergotamin (the "gynergene" preparation); hypercholesterinemia resulted. The author concludes that the production of cholesterin takes place in the suprarenals, ovaries and spleen, and that the straightening or weakening of the functions of these glands of internal secretion through the nervous system is the cause of the hypercholesterinemia or hypocholesterinemia in the subjects of the experiments.

Epithelial Repair in Recovery From Vitamin A Deficiency.—WOLBACH and HOWE (*J. Exp. Med.*, 1933, **57**, 511) have studied minutely and recorded the process of repair of epithelium in recovery from vitamin A deficiency. In their opinion absence of vitamin A causes a starvation specific for many epitheliums. This results in an atrophy and finally in the formation of a stratified keratinizing epithelium regardless of the morphology of the original epithelium. As had been shown previously, this metaplasia is the earliest demonstrable effect of vitamin A deficiency in rats. They found that correcting the vitamin A defi-

ciency in the diet before metaplasia was complete resulted in a rapid restoration of an epithelium identical in morphology with the original epithelium, before the deficiency diet was instituted. In rats in which the process of metaplasia was completed, by keeping the animals on a diet deficient in A for a suitable length of time, they found the process of repair to consist of a vascular degeneration of cells, the upper stratum disappearing by lysis while the lower stratum developed into cells normal for that location. Permanent loss of identity of an epithelium may occur where infection has occurred in cysts or in cases of cicatrized glands. The authors conclude that since the cells of the stratum germinativum preserve the identity of the original epithelium, that this identity is contained within the nuclear chromatin, which is, therefore, unaffected by the deficiency. It is noteworthy that the authors' series of rats were remarkably free of infection, and this gives support to the statement that the condition of vitamin A deficiency does not increase susceptibility to infection by bacteria.

HYGIENE AND PUBLIC HEALTH

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A Study of Tuberculosis Among the Indians in Montana.—CROUCH (*U. S. Pub. Health Rep.*, 1930, **47**, 1907) states that in Montana the death rate from tuberculosis among the Indians is about 15 times as high as among the whites. Among mixed bloods the tuberculosis death rate is much lower than among full-blood Indians. When tuberculin-tested (Mantoux) the figures for positives among children was as follows: Full-blood, 75 per cent; mixed blood, ¼ and more Indian, 54.3 per cent; mixed blood, less than ¼ Indian, 39.3 per cent; whites, 22.6 per cent. Furthermore, it was shown that above the age of 17 years all full-blood Indians tested were positive, while mixed-bloods showed lower figures of positives than in earlier years. The question of race susceptibility is not settled, but it is suggested that complete healing is less frequent in full-blood Indians.

The Preparation of a Vaccine From Fleas Infected With Endemic Typhus.—DYER, WORKMAN, RUMREICH and BADGER (*U. S. Pub. Health Rep.*, 1932, **47**, 1329) review the preceding work on typhus and Rocky Mountain spotted fever and record the results of their own experiments. Fleas of the species X. cheopis infected by feeding on white rats were emulsified and the potency of the emulsion tested on guinea pigs. The virus then was destroyed by the addition of phenol

and used to inoculate guinea pigs. Some protection was shown when the immunized animals were later inoculated with living typhus virus together with a suitable number of control animals.

Duration of Viability and Virulence of Bacillus Pestis.—FRANCIS (*U. S. Pub. Health Rep.*, 1932, **47**, 1287) subjected a single strain of B. pestis to 4 tests of duration of viability and virulence. Pure, undiluted, neutral glycerin at −15° C. was used for suspending the spleen of a plague guinea pig in one test, while a pure culture of B. pestis isolated from the same guinea pig was suspended in glycerin at −15° C. in another test. The bacilli in the spleen were viable and fully virulent at the end of 7 years, while the glycerinated pure culture was fully virulent for 14 months, slightly virulent for 2 years, 7 months, and dead at the end of 3 years, 5 months. A plain agar culture of B. pestis was stored at 10° C., sealed and unopened, for nine years in 1 test, while in another test a plain agar culture was subcultured every 3 months for 9 years along with other cultures in a general collection of stock cultures stored at 10° C. The result at the end of 9 years was viability and full virulence of the sealed culture, but viability and nonvirulence of the stock culture.

The Social Incidence of Rheumatic Heart Disease. A Statistical Study in Yale University Students.—PAUL and LEDDY (AM. J. MED. SCI., 1932, **184**, 597) found the incidence of rheumatic heart disease in a group of 7914 undergraduate students of Yale University to be 8.2 per 1000, as compared with 15 per 1000 which is an average figure obtained from statistics of comparable age groups of individuals in other walks of life. Among the men in this group who had attended expensive boarding schools the incidence was only 5.8 per 1000 as compared with 12.5 per 1000 among those from high-schools. The contention that rheumatic fever is a disease which finds a lower incidence among people of ample means finds support in these observations. According to the methods employed the factor of poverty does not, however, seem to be as important a predisposing rôle in determining the incidence of rheumatic heart disease as it does in clinical tuberculosis.

The Prevention of Rickets.—MITCHELL and COLEY (*J. Am. Med. Assn.*, 1932, **99**, 1768) conclude from their studies of a group of 139 babies over a period of 2 years that either cod-liver oil, in doses of 2 or 3 teaspoonfuls daily, or viosterol, in doses of 8 or 10 drops daily, exert a definite influence against the development of rickets, and by either treatment severe or even moderately marked rickets is prevented in babies who live in good hygienic surroundings. In spite of the aforementioned therapy, 22.3 per cent of patients show clinically mild rickets. In 15.9 per cent of the cases the Roentgen findings were positive. The administration of cod-liver oil in the dosage mentioned completely protects 82 per cent of the patients, while the given dose of viosterol completely protects only 75 per cent, in spite of the fact that the amount of viosterol has a little more than twice the amount of vitamin D contained in the daily dose of cod-liver oil. The lowest prevalence of rickets, 9.9 per cent, occurred among those given sunbaths in summer and viosterol or cod-liver oil in winter. The ultra-

violet ray is a satisfactory substitute for sunbaths, the incidence of rickets in those so treated being 13.6 per cent. In the causation of rickets there must be other factors than a deficiency of vitamin D—a comparative deficiency of vitamin A as expressed by De Sanctis and Craig, a deficiency of minerals in the diet as suggested by Weston, or perhaps some other as yet unrecognized agent in which the influence of light possibly plays as important a part as it does in the activation of ergosterol.

Oysters and Anemia.—COULSON, LEVINE and REMINGTON (*Am. J. Pub. Health*, 1932, **22**, 1141) report results to show that the oyster is equalled or excelled only by liver in the amounts of iron and copper which it may furnish to the diet in an average serving. That these metals are easily available for hemoglobin production has been shown in previous work in which it was found that oysters, oyster ash (acid soluble) and a solution of iron, copper and manganese in the same quantities, fed to anemic rats, brought about hemoglobin regeneration at the same rate in all 3 cases. Oysters should, therefore, be efficacious in the treatment or prevention of those types of secondary anemia which respond to treatment with iron, or iron plus copper. There is increasing support for the view that dietary deficiencies can best be corrected by proper selection of foods, rather than by the use of artificial concentrates or medicinal mixtures. In order to insure an adequate supply of the inorganic constituents for hemoglobin production it would seem a wise plan also to include oysters in the diet of the pernicious anemia patient in conjunction with liver extract, since it is known that liver extract is relatively low in iron. An average serving of oysters (110 gm.) would furnish about 2 per cent of the human calorie requirement (3000 calories), and yield about 40 per cent of the daily dietary standard for iron, stated by Sherman to be about 15 mg.

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